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И РОССИЙСКОГО НАЦИОНАЛЬНОГО ИССЛЕДОВАТЕЛЬСКОГО МЕДИЦИНСКОГО
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МЕДИЦИНСКАЯ ЭТИКА

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# THE ETHICS OF PERSONALIZED MEDICINE

Savelyeva MI ✉

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The early XXI century was marked with entry into the market of a great deal of medicinal preparations with a totally new molecular-oriented mechanism of action. These results could only be made possible through achievements in molecular and cellular biology and completion of the Human Genome Project, in particular. Many pathogenic mechanisms of different illnesses, including oncological and autoimmune ones, were deciphered. The data stimulated the search for totally innovative therapy methods targeting at the key links of the abnormal process pathogenetic chain, collectively known as 'targeted therapy'. The issues of personalized medicine, including the ethics, are considered through the study of the Coriell Institute.

**Key words:** personalized medicine, genetics, genomics, targeted therapy

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# ПЕРСОНАЛИЗИРОВАННАЯ МЕДИЦИНА С ТОЧКИ ЗРЕНИЯ МЕДИЦИНСКОЙ ЭТИКИ

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Начало XXI века ознаменовалось выходом на мировой фармацевтический рынок большого количества лекарственных препаратов с абсолютно новым молекулярно-ориентированным механизмом действия, что стало возможным благодаря достижениям в области молекулярной и клеточной биологии, в частности, завершению проекта «Геном человека». При этом удалось расшифровать многие механизмы патогенеза различных заболеваний, включая онкологические и аутоиммунные. Появление этих данных явилось стимулом для поиска принципиально новых методов терапии, точечно воздействующих на ключевые звенья патогенетической цепи патологического процесса, получивших в связи с этим общее название «таргетная терапия». На примере исследования института Coriell рассмотрены проблемы персонализированной медицины, в том числе в аспекте медицинской этики.

**Ключевые слова:** персонализированная медицина, генетика, геномика, таргетная терапия

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Personalized medicine is a new paradigm in biomedicine. Its successful implementation requires integration of unprecedented information volume and various communities, not only professional ones. The ability to collect, analyze, exchange and integrate an enormous amount of biological and clinical data on a real time basis is a prerequisite of personalized medicine.

Biomedicine is a complex system with key interrelations between the sectors. The objective of personalized medicine is transformation of this system, that's why it's necessary to acknowledge and accept its complexity. Key possibilities to create a self-sustained subsystem of personalized medicine arise owing to understanding the flows of resources and data within a larger system of clinical medicine.

Threatening complexity of the personalized medicine subsystem makes the use of information technologies critically important. However, information technologies as part of the biomedical community are being developed slowly, and they rarely connect laboratories even within the same institution, much less those at various institutions.

Thus, to solve complex issues of oncological diseases and eliminate similar gaps in the research process, the biomedical society of the XXI century requires implementation of inter-operability, i. e., access to integrated instruments to collect, analyze and exchange data in standardized formats. The inter-operability is a tool that unites all scientists, clinicians, patients and other participants to ensure fast exchange of the standardized information.

Personalized medicine needs data exchange. This should be implemented through the best practices in the sphere of information technologies. Information technology applications are randomly divided into approaches used to connect data and the ones to connect people.

The key advantage of personalized medicine complete subsystem conceptualization is an ability to turn biomedicine into the educational system. More precisely, a synergistic union of studies, provision of medical aid, quality assessment, measurement of effectiveness and safety of the used medicinal preparations is possible, while covering the entire life cycle of biomedicine.

Personalized medicine means that prognoses, predictions, diagnostics and therapy are adapted to certain individuals considering their biological features. Then it can be warranted that a certain individual will undergo certain activities at a certain time. For this, not only medical technologies, but also a better information infrastructure, improved integration of clinical and research efforts, constant innovations in medical education and, finally, deep relation with a patient who becomes a partner in obtaining the medical aid need to be developed.

## ONCOLOGY AS A PIONEER OF PERSONALIZED MEDICINE

Researchers of oncological diseases were at the leading edge of personalized medicine revolution and many first-generation medications (tamoxifen, imatinib, etc.) of personalized medicine

were developed for their treatment. The reasons for this phenomenon were as follows.

1. Oncopathology is a complex set of diseases. Approaches to their examination with the help of molecular medicine occurred before the Human Genome Project. At the end of the XX century, it was known that oncopathology was caused by genetic changes, both inherited, and acquired, leading to abnormal cellular proliferation, slow induction of apoptosis, metabolism activation, neoangiogenesis and metastasis.
2. Oncopathology is a serious and frequently deadly disease characterized by very low effectiveness of therapeutic medications. As selection of the most effective treatment can be an urgent decision associated with life or death, approaches to personalized medicine as compared with the time-consuming trial-and-error method have obvious advantages.
3. Side effects of anti-tumor therapeutic agents are rather unpleasant, they often mutilate a patient and are potentially lethal. That's why it is even more important to select an optimal therapy at the first visit to avoid double negative unfavorable effects due to useless treatment.

For instance, the National Cancer Institute (NCI) has a unique set of administrative platforms that embrace the entire life cycle of biomedicine development and create a unique environment that can serve as a prototype of the personalized medicine paradigm. For 50 years the NCI has been supporting complex oncological centers that combine scientific research, provision of medical aid and prevention. There exist over 60 similar centers distributed over the country and located in the most prestigious research and therapeutic institutions of the USA. The NCI has over 50 Specialized Programs of Research Excellence (SPOREs) that support translational studies and 10 Cooperative Group programs that conduct multi-institutional clinical trials. As far as the medical aid goes, the NCI has launched the Program of Public Oncological Centers (NCCCP) with 16 objects and 20 million people.

In 2003, the NCI decided to integrate unprecedented information technologies into the biomedical society due to three factors such as the growing clinical and economic burden of oncopathology, transformation of trials, acting as a catalyst for molecular revolution, and numerous technologies of genomics that generate enormous amount of data and accept that 'the essential unity' of trials and clinical aid can improve the outcomes in all types of oncopathology, just like it was done with pediatric oncology. As the first step in creating the infrastructure of informatics that would enable medicine personalization, the NCI officially launched the pilot caBIG® (cancer Biomedical Informatics Grid) initiative in 2004. Its primary objective was to develop the possibilities that would correspond to certain requirements of the NCI oncological center society (more detailed data about the history of caBIG® see in the caBIG® pilot phase report at http://cabig.cancer.gov/resources/report.asp.)

Though the revolution in molecular biology occurred in the late XX-early XXI centuries, the target concept was formulated by Paul Ehrlich, a German scientist, in the beginning of the last century. He believed that a target is an enzyme (or any other biological molecule, organelle, physiological feature, etc.) present in a pathogenic microorganism, which is being essential for vitality of the latter, but absent in a patient's body. Thus, the medications specifically inhibiting target molecules should have an extremely wide therapeutic index. For instance, they can display high antibacterial activity with the least number of adverse effects. Traditional antimicrobial agents such as antibiotics, antimycotics, antivirals agents, etc., are based on a similar principle. Anti-tumor agents should have equivalent properties, but differences between mutated and initial cells are more sophisticated and complicated as compared with differences between bacteria and a human being [1]. A new generation of medications (the so-called targeted antitumor agents) were developed in the late XX century only due to rapidly progressing molecular oncology [2].

## ISSUES ASSOCIATED WITH IMPLEMENTATION OF PERSONALIZED MEDICINE

Personalized medicine uses the underlying genomic/genetic information about a patient to predict the risk of diseases, diagnose the existing pathology, prevent adverse reactions to medicinal agents and adapt to treatment (fig. 1) [3–5].

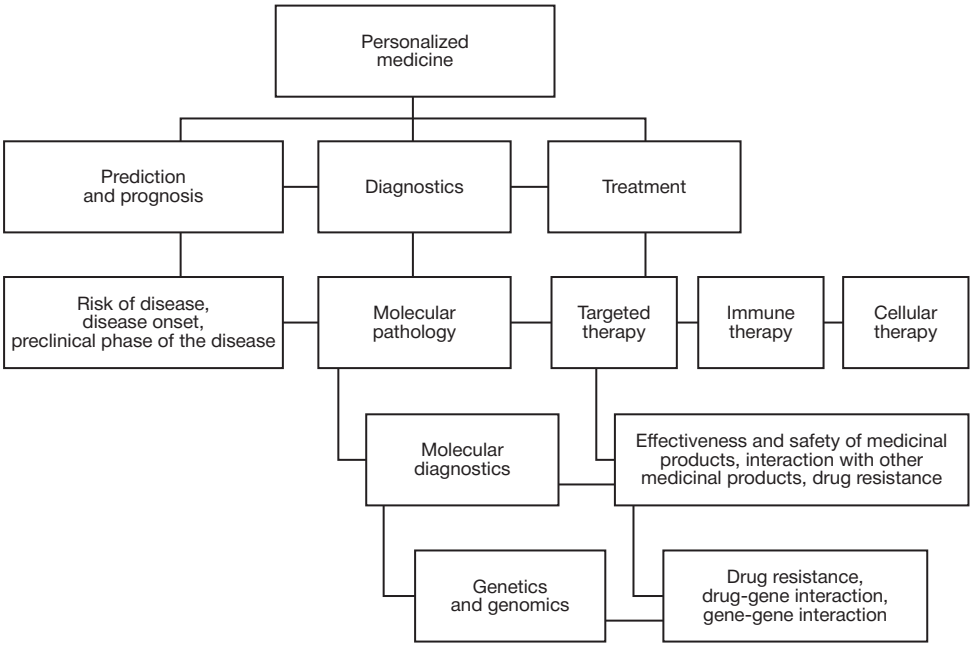


**Fig. 1.** Scheme of the structure of personalized medicine

Successful implementation of personalized medicine depends on several factors. First, there exists an acute need in teaching medical professionals detailed genetics [6–9]. The volume of genetics commonly taught at medical universities is limited. It deals with monogenic disturbances and chromosomal abnormalities, whereas students know nothing about complex genetics.

Second, integration of personalized medicine requires state support and regulatory surveillance [10–12], and public discussion of ethical issues [13, 14]. Third, systems of medical documentation need to be structured in such a way as to ensure that they accept genetic data and integrate them into the existing medical record of a patient. Then they will be used while taking clinical decisions.

Additional issues for evidence-based studies of personalized medicine effectiveness include the need to form large cohorts and collect longitudinal data for the database used to calculate treatment effects and estimate potential expenses and benefits. The cohort must be rather large to consider as follows:

1) genetic variations with low incidence (1–2%),
2) influence of a gene on the environment;
3) gene-gene interrelation; 4) last observation carried forward.

Large cohort studies also come across the issues of consent and confidentiality [15]. Moreover, genetic studies in larger cohorts require significant infrastructure of biobanking, genotyping and information technologies [16].

**Importance of biobanking**

Biobanking includes collection, characterization, storage and distribution of valuable biomaterials and associated research data. Biobanking is used to create and support bioreservoirs as national and international resources to study human disorders and ageing. Regular expansion of data management systems is necessary, including web-catalogue of biomaterials and related data. That's how there will be correspondence with the changing business and scientific requirements.

The possibilities of biobanking include significant management of phenotypic data using the standardized phenotypic language and collection of longitudinal data for a set of diseases [17, 18]. Moreover, cooperation with several regional healthcare systems is possible. Their rapid transition to complex systems of electronic medical records is possible. This will allow active completion of tasks associated with implementation of genomics into clinical practice.

## SEARCHING THE WAYS OF DEALING WITH PROBLEMS OF PERSONALIZED MEDICINE

The Human Genome Project [19], SNP Consortium [20] and HapMap Project [21] laid the foundation for the next generation of efforts regarding genetic mapping of complex diseases and quantitative trait loci (QTLs) [22], which can be preclinical indicators of a potential disease. To make the data useful for health and quality of life improvement, it is necessary to create a mechanism of exchanging data about genetic variations associated with complex diseases, people and suppliers of medical services, and conduct scientific-based trials to estimate the results of the data obtaining and usage.

The Coriell Personalized Medicine Collaborative (CPMC) is a study that utilizes a scientifically substantiated approach to determine the value of using personal genomic data to control health and take clinical decisions.

The CPMC objective is to form a cohort with extensive genotypic and phenotypic data that can be used to find genetic variations influencing toxicity and effectiveness of medications and detect currently unknown gene variations that increase the risk of oncopathology and other severe diseases.

The study involves doctors, scientists, ethicians, genetic consultants, voluntary study participants and experts in information technologies, with the common task of better understanding of the effect of personalized or genome-informed medicine and ensuring its ethical, legal and domestic implementation. By the end of 2009, 10,000 people participated in this study, with 100,000 of participants being an ultimate purpose.

The global purpose of the CPMC is to become a model of ethical, legal and responsible implementation of personalized genome-based medicine. The CPMC study provides the dynamic connection between Coriell and study participants via the protected web-portal.

Web interviews are used to estimate health and personal data about genetic variations obtained during the study. Moreover, participants can share the data with medical professionals via this portal. The CPMC is currently funded from voluntary donations and institutional support with no costs for study participants.

When the informed consent is obtained, participants are requested to provide two ml of saliva for genome profiling using a microchip platform (Affymetrix 6.0 Genechip, Affymetrix, Santa Clara, CA) and target SNP profiling using a bead-based platform (Illumina BeadXpress, Illumina, San Diego, CA). The external group of experts (Informed Cohort Observation Board (ICOB)) meets at least twice a year to consider genetic variations provided by Coriell as health risk options.

Only genetic variations associated with health conditions which are considered potentially suitable for medical actions (when the risk can be reduced and the variations with a significant reproduced association) are later returned to participants via the protected web portal.

Participants can provide access to the doctor (doctors) to review the results and can request a free discussion of the results with the CPMC genetic consultant. Various results are estimated through web interviews where participants assess their own actions, actions of their doctors and their health conditions. The participants are asked to update data regarding health, family and way of life, because that is how longitudinal data are created. Thus, there exist several dynamic aspects of the CPMC including constant analysis of associative studies to reveal genetic variations and submit them to the regulatory authority (ICOB), constant examination of the obtained results and annual longitudinal collection of participants' medical records.

## INVOLVEMENT OF HOSPITAL PARTNERS AND MEDICAL PROFESSIONALS

As far as the task of genomic data integration into medical practice goes, education of medical professionals, especially doctors and nurses, will probably be a restrictive step. The Coriell Institute is aware that involvement of clinicians and other medical professionals is important to develop successful integration strategies of complex genetic data into the modern medical paradigm. The Institute does the same by including them into the CPMC as coauthors and participants. Moreover, the prevalence of oncopathology in the society, and the huge potential of influence of personalized medicine on research and treatment of various types of cancer are highly estimated. That is why Coriell established cooperation with adjacent medical institutions to conduct the CPMC study. The Coriell Institute encourages participation of medical professionals and

employees of medical centers in the research. These relations activate the study and offer opportunities to teach medical professionals genomics.

One of the educational strategies of medical professionals will include seminars conducted by Coriell scientists and doctors from hospitals in partnership. The seminars are devoted to diseases included into the CPMC, and correspond to the requirements of continuous medical education (CME) enabling access to CME credits.

Trying to make education more affordable for medical professionals, Coriell company can provide access to seminars in genomic medicine via webcasts over the Internet.

Implementation of genomic medicine requires bilateral exchange, where scientists will teach medical professionals, and vice versa. The exchange will include traditional communication in addition to exchange with medical and genetic data (as electronic medical records and a great number of genetic testing results respectively). Coriell expects that deep involvement of several hospitals into the CPMC will be a catalyst for this dialogue. Moreover, it is suggested that as soon as the CPMC participants will invite medical professionals to learn about their personal genetic results, Coriell will have an involved and accessible population of medical professionals, among whom they can conduct focus-group interviews regarding the use of genomic information while providing medical service.

## ENROLLMENT OF PARTICIPANTS INTO THE CPMC STUDY

People are enrolled in the CPMC study mainly during the informed consent sessions conducted at the Coriell Institution, hospitals in partnership and other public establishments. The principal researcher of CPMC or CPMC scientist discusses the study results, possible risks, content of the informed consent document and gives the participant a possibility to ask questions. When the informed consent form is signed, new participants are offered to give a small sample of saliva.

Requirements to participants are as follows: they must be over the age of 18, have a valid E-mail address and readiness to participate in interviews for several years. The participants can take a decision (during registration or at any time after that via the protected web portal) to present their unidentified genomic data about variations and case history to the scientific society to conduct associative studies. The CPMC study is free for participants.

## ONCOLOGICAL DIRECTION OF THE CPMC

As Coriell is a partner of medical centers, including Fox Chase oncological center, it can conduct a study in addition to the abovementioned health direction. The first 10,000 participants involve 2,500 patients with breast cancer and 2,500 patients with prostatic cancer. There is some evidence that the primary risk of cancer strongly depends on genetic variations, and that in oncological patients, reaction to chemotherapeutical agents, medication associated side effects and clinical outcomes depend on genetic peculiarities of the patient.

Thus, formation of a large cohort of patients with breast and prostatic cancer, extensive phenotypic data from the national registries of these types of cancer and genomic/genetic data will allow researchers to examine the role of genetic variations at pharmacogenomic and clinical endpoints. The wide scientific society will get access to the unidentified data provided to the CPMC by participants via the database of genotype and phenotype (dbGaP) of the National Center of Biotechnological Information.

## THE REGULATING AUTHORITY: INFORMED COHORT OBSERVATION BOARD

The Informed Cohort Observation Board (ICOB) estimates medical feasibility of health conditions and proof of potential medical feasibility of a genetic risk variation regarding this health (disease) condition. The principal condition to consider genetic variations is validity of association studies published in the literature. They demonstrate a significant relation between genetic variations and certain abnormal conditions. Thus, the ICOB determines which personal data about genetic variations will be returned to the study participants.

Approval is provided when knowing the participant's status regarding a certain genetic variation will influence the course of treatment assigned by a medical professional or will enable to provide an advice about health or way of life which promotes risk reduction. By using perspective web interviews, the CPMC study will help to determine whether the use of data about the variation reduces the risk.

The external advisory board includes recognized scientists, medical professionals, specialist in ethics and a pastor of a parish. The Board concept was offered by D-r Kohane et al. [23]. The approach is a model of the national system estimating genome-informed medicine.

The CPMC scientists study medical and scientific literature to reveal the variations of candidate genes and submit brief reports to the ICOB. The ICOB reviews every report and votes for approval, disapproval or request of additional data for every variation and condition. The factors that need to be considered include as follows:

- recommendations of the Food and Drug Administration of the USA (FDA), centers for disease control (CDC), national healthcare institutions, national associations of medical specialties or other government consultation bodies;
- severity of a disease, condition or potential unfavorable reaction to a medication;
- number, scope and quality of research that demonstrate statistically significant relation between the gene type and the disease. Meta-analyses (if any) are considered as well;
- the size of an effect of a certain genetic variation;
- risks and advantages of clinical interventions or interventions associated with the way of life to reduce or decrease the risk;
- data elements to measure results.

The ICOB's assertion means that the relation between the genetic variation and health condition was confirmed and the condition is considered as potentially suitable for medical application. The assertion does not require robust evidence stating that the variation is useful for influencing the treatment outcomes. The CPMC task is to submit the outcomes in order to determine the usefulness of every genetic variation.

The ICOB meets at least twice a year. The frequency allows to integrate the results of the reviewed association studies, find new associations and confirm the previous outcomes.

It is quite likely that the CPMC will later ask the ICOB to consider both previously declined variations with new scientific proof, and previously declined conditions of health in relation to which prevention or treatment possibilities changed the potential ability to act. The ICOB decisions are taken by the majority of votes. In a group, discussions are held in a closed regimen. It is warranted that scientific issues are discussed in the objective, critical and unburdensome setting. However, all discussion outcomes are manifested via the web portal.

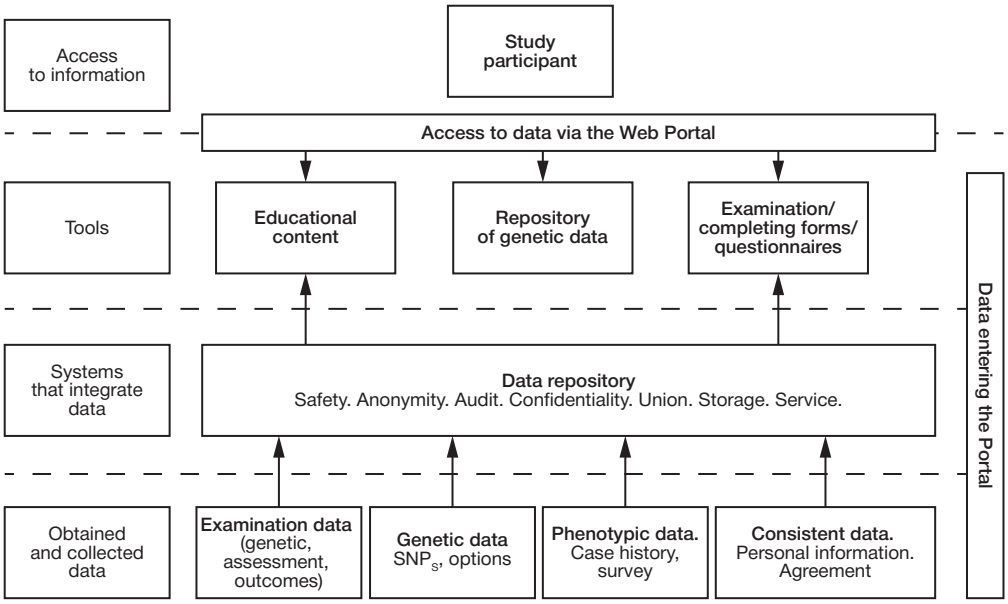


**Fig. 2.** Architecture of the CPMC research web portal

## DYNAMIC INVOLVEMENT OF PARTICIPANTS: THE RESULTS ARE VIEWED THROUGH THE PROTECTED WEB PORTAL

The CPMC web portal is a web site with several functions. It allows to:

1) collect data using online interviews,
2) report the results of genetic variations,
3) educate participants and medical professionals,
4) safely share personal information about genetic variations with medical professionals,
5) request access to data from scientists via the Internet;
6) request genetic counselling from participants via the Internet.

It is a public site with a portal that enters the protected server. In the protected part of the site, participants can configure the CPMC account with a password, change contact data (E-mail address), update the consent options (consent to present their unidentified data for genome wide association studies (GWAS)) and review data about personal genetic variations as they become available.

Moreover, the CPMC web portal has a significant number of materials regarding genetic education. These materials are written for two different audiences such as non-professionals and medical professionals though any person can get access to more advanced educational materials. Educational pages include data about basic genetics and such important scientific events as the Human Genome Project and HapMap Project. Educational materials about inheritance, types of oncopathology, multifactorial nature of complex diseases, the term of 'risk' and interpretation of disease risk estimation, and the reasons for which the research is possible today only.

Every time participants visit the web portal, they are involved in the process anew. They need to review the results of every genetic variation on their own. It warrants that the results are controlled by the participant, and that the participants are not informed about the results they are not actively searching for. The persons who decided to review the CPMC results will see a short educational video where a genetic consultant will give preliminary recommendations about this issue before revising data about the personal genetic variant. The CPMC will encourage participants to invite their treating physicians to see the results. The participants can provide access to their results using their accounts on the CPMC web portal.

Moreover, the site provides actual data about the possibilities for participants such as the study related free genetic consultations, educational forums and additional interviews. The CPMC can display data about other researches participated by the subjects. The scheme of information system architecture is presented in figure. 2.

Personal information is decoded and stored separately from the genotype and medical information. This is how data confidentiality is preserved. Two factor safety is used for dynamic creation of web pages, while participants are viewing their personal data.

## REALISTIC RISKS: EXPLAINING THE VALUE OF RISK INCREASE

The CPMC tries to report the realistic risks related to genetic associations using the format which is easily comprehended by non-specialists. All presented results will show the known population risk of a disease (specific for race/gender/age-related groups, if any) and corrected risk based on the genotype of a genetic variation.

Though in some cases a certain genotype can significantly increase the risk, it is expected that the majority of genetic variations associated with complex (multifactorial) diseases will result in insufficient increase of the risk. Until the algorithms for the union of risks associated with more than one genetic variation are verified, each of them will be presented separately. All reports about the results include references to basic literature sources.

To make participants and medical professionals comprehend the risks associated with genetic variations included into the CPMC results, an educational section 'Comprehension of chances' was created on a web portal. In this section written both for non-professionals and medical workers, a concept is described, in accordance with which the risk of complex diseases is dynamic and includes an interrelation between genes and environment.

Moreover, a genetic investment in a complex disease is discussed, the likelihood that the genetic risk of a complex disease is influenced by dozens of separate genes, but not the

only and currently reported variation, is considered, and the results are reviewed. It is also explained that considering the current level of knowledge, family history is probably the more significant factor of risk of the majority of complex diseases as compared with one genetic variation.

## COMPREHENDING THE RESULTS: GENETIC COUNSELLING

In the epoch of genomics and personalized medicine, genetic counselling requires a new approach to one gene-associated violations, which should be different from traditional counselling [24]. Coriell employs certified genetic consultants involved in the CPMC study who are ready to provide genetic counselling via E-mail, by phone or during personal consultations in the office and on educational forums which are open for the CMPC participants. Medical professionals whose patients participate in the study can also request access to genetic counselors of the CPMC to discuss the study and data about genetic variations. Genetic counselors will register all meetings with the CPMC participants using the password-protected database accessed by the CPMC genetic counselors only. Owing to the data base, genetic counselors will have an easy access to the history of contacts between them and participants. Then the counselors can trace the amount of time and type of conducted consultations, and collect statistical data by types of diseases and variations for which consultations are requested. The tracing system will also enable to find common areas of concern, which can be used in future to educate both common citizens, and medical professionals.

## MEDICAL HISTORY, FAMILY HISTORY AND WAY OF LIFE QUESTIONNAIRES

Participants must fill in extensive medical history, family history and way of life online questionnaires after the personal account was created in the CPMC. The questionnaires should be filled in before the genetic results are reviewed. The participants will be offered to update medical history, family history and way of life data one year after the data were introduced and then every twelve months. The data will be used for two purposes: 1) combined with genotype data to calculate the personalized risk, when possible, 2) combined with genotype data in GWAS studies to detect additional genetic variations that promote development of complex diseases and/or metabolism of medications (for those participants who permitted the use of their unidentified data for association studies).

Coriell accepts the importance of CPMC data in GWAS studies. It created a mechanism (via the participant's consent form) that enabled participants to inform about their will to submit unidentified data to researchers (both to non-commercial, and commercial organizations). Thus, unidentified CPMC data will be provided to all certified researchers via the NCBI dbGaP web portal.

The model is to conduct interviews via the web portal enabling a crosscheck of data through various questionnaires. The longitudinal nature of this project, constant publication of genetic variation results and request of annual interview data update allows to collect data which are commonly difficult to obtain such as the regimen of nutrition and physical load over time and environmental influence as far as they arise.

## LONGITUDINAL DATA COLLECTION: ELECTRONIC MEDICAL RECORDS

The subjects can select the last medical records from their supplier of primary medical aid in printed or electronic form if they are located in the system of electronic medical records (EMR) of the hospital in partnership. The updated medical records will be requested annually to ensure longitudinal data collection. The datasets will be traced to detect changes in health values associated with the diseases for which the CPMC submitted data about genetic variations. Medical records will be compared with self-reports of patients about their case histories.

The CPMC employees will decode part of information from the medical record and place it into the personally controlled medical record for every subject. All systems of information technologies by Coriell will ensure compliance with the standards of operational compatibility (HL7) and definitions of medical data such as SNOMED and LOINC.

## CONFIDENTIALITY AND SAFETY OF PARTICIPANTS

Coriell has a number of provisions to support the integrity, confidentiality and safety of data and information systems at its disposal. At Coriell, the policies of safety warranting protection of all data from unauthorized access are valid; audit logs, procedures of backup and error checking are supported. This is how the CPMC data are made accurate and protected. Data safety is a balanced combination of actions by the authority and personnel, operational activity and measures of technological control.

The infrastructure of the CPMC information technologies includes three highly-integrated technological levels:

1) web portal,
2) system of managing laboratory information to control disposable material, phenotypic data and processes,
3) protected hardware infrastructure containing servers of web applications, servers of databases, storage arrays and network security devices. Personal identifying data is decoded and stored in a data base separate from a genotype and medical data. Subjects shall have to enter the protected web portal using the bar code identifier, user name and secure password.

## ACCESSIBILITY OF CPMC DATA FOR RESEARCHERS AROUND THE GLOBE

The CPMC team and the National Institute of Human Genome Research discussed the strategy of displaying unidentified data of the CPMC participants who decided to share their data with scientists to conducts research via the dbGaP web portal. The Coriell Institute endeavors to provide a wide access to the valuable set of data. The Institute has been placing the data on dbGaP portal for a long time so that they could be used by certified scientists. It also participated in return of genotypic data based on samples of Framingham Heart Study from the depositary of the National Institute of Neurological Diseases and Stroke, and National Institute of Common Medical Sciences at Coriell.

## OUTCOME STUDIES

The subsequent studies of actions of the CPMC subjects and medical professionals and participants' health outcomes form the basis of this evidence-based study. Thorough initial estimation of medical history, family history and way of life is carried out prior to announcing the results of personal genetic variations. Moreover, subjects can check the initial knowledge of genetics.

In respective scaling, CPMC-collected data will be used to estimate whether healthcare expenses are increased due to implementation of genomic medicine by using the objective

criteria such as a number of visits for treatment, prescribed analyses, hospitalization-based data and prescription for medications. The values of medical practice based on physician opinions and recommended practices will be balanced by way of studying the choice made by the participants dealing with different options of medical service. Coriell will develop these values in cooperation with hospital partners and such companies as the Center for Technology Assessment to ensure monitoring of the respective elements of clinical data.

## CONCLUSION

The CPMC is a new model of translational medicine, evidence-based study, intended to determine which elements of personal genetic data are valued while taking clinical decisions and obtaining results of health care. The web portal containing medical records and genomic data is highly dynamic due to constant update of data base and possible continuous improvement of education in the sphere of genetics/genomics of all system participants. Meanwhile, CPMC participants can get access to the web portal and participate in the study free of charge. Unidentified genotypic and phenotypic results of participants who decided to release their data will be available to certified scientists for subsequent analysis.

Close collaboration with municipal hospitals, and not large clinical centers only, encourage participation of physicians in personalized medicine.

The programs will enable to build a foundation of the new type of healthcare in order to:

- implement the new model of translational medicine;
- form a subsystem of subjects that would unite researches, provision of medical aid and health data;
- destruct traditional isolated structures, which represent barriers for rapid discoveries and acquisition of knowledge;
- accelerate and increase the productivity of studies and improve clinical outcomes.

Development of these programs in the Russian Federation and their proper financing would enable fast introduction of the principles of personalized medicine into real clinical practice and notably oncology where the demand is significantly higher as compared with other areas of medicine.

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# LEGAL AND ETHICAL EXPERTISE OF GENETIC RESEARCH: ISSUES OF REGULATION AND INSTITUTIONALIZATION

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Although legal regulation of genetic research has been steadily improved, it is still lagging behind promotion of genetic research, especially in the field of development and use of its achievement-based technologies. A distinct feature of this legal area is currently a higher dependence on ethics. This resulted in establishment of a special institution, an ethics committee, that unites the possibilities of ethical and legal expertise giving birth to numerous organizational and substantive issues. Some of them are reflected in discussions about the relationship between moral reflection and legislative processes, epidemiological status of bioethics, etc. For instance, in Russian literature there is a thesis that organization and conduction of ethical expertise is regulated much better than those of legal one and can be implemented within the current legal and regulatory framework. Meanwhile, a need for legal expertise in genomic research and genetic technologies is not inferior but even superior. This is confirmed by deficient legal support of many important decisions taken by the authorities and actions accomplished by research groups. The article reviews opinions of Russian and foreign scientists who provide different assessment of the role of ethics committees and their possible falling within law or ethics. The role and place of ethics committees in the system of rule-making harmonization and law enforcement are specified.

**Keywords:** genetic research, bioethics, ethical committee, ethics-consistency review, code-consistency review

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# ПРАВОВАЯ И ЭТИЧЕСКАЯ ЭКСПЕРТИЗЫ В СФЕРЕ ГЕНЕТИЧЕСКИХ ИССЛЕДОВАНИЙ: ПРОБЛЕМЫ РЕГЛАМЕНТАЦИИ И ИНСТИТУЦИАЛИЗАЦИИ

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Правовое регулирование генетических исследований неуклонно совершенствуется, но все равно не успевает за развитием самих генетических исследований, особенно в сфере разработки и применения основанных на их достижениях технологий. Отличительной чертой данной области права в настоящее время является его более высокая зависимость от этики, что выразилось в создании особого института — этического комитета, объединяющего возможности этической и правовой экспертизы, но одновременно с этим рождающего многочисленные проблемы как организационного, так и содержательного характера. Некоторые из этих проблем отражаются в дискуссиях о соотношении этики и права, эпистемологическом статусе биоэтики и др. Так, например, в отечественной литературе высказывается тезис о том, что организация и проведение этических экспертиз в отличие от правовых регламентировано значительно лучше и может осуществляться в рамках действующей нормативно-правовой базы. Между тем потребность в правовой экспертизе в области геномных исследований и генетических технологий никак не меньшая, если не большая, что подтверждается дефицитом правового сопровождения многих важных решений власти и действий исследовательских коллективов. В статье приводятся мнения отечественных и зарубежных ученых, расходящихся в оценке полномочий этических комитетов и возможности их отнесения к сфере права или морали. Уточняются роль и место этических комитетов в гармонизации системы нормотворчества и правоприменения.

**Ключевые слова:** генетические исследования, этическая экспертиза, правовая экспертиза, биоэтика, этический комитет

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Concerned that legal regulation of genomic research should be developed and that genetic technologies should be applied, Russian legislators have adopted Federal Law as of 12 April 2010 No. 61-FZ 'On Medicine Circulation' implementing the best global practices. In particular, the legislators have improved regulations and mechanisms of expertise production that provide for special expertise structures, Councils of Ethics. The Law prescribes a list of basic requirements to experts, provision about the council, procedure of its activity, organization and production of an ethical expertise. There is also another document, Executive Order of the Ministry of Health and Social Development of the Russian Federation as of 26 August 2010 No. 753н 'On Approval of the Procedure of Organization and Conduction of an Ethical Expertise of Possibility to Conduct a Clinical Trial of a Medicinal Product for Human Use and Form of Conclusion from the Ethics Council', regulating the same (registered in the Ministry of Justice of the Russian Federation as of 31 August 2010 No. 18303).

Another Federal Law as of 21 November 2011 No. 323-FZ 'On Fundamental Healthcare Principles in the Russian Federation' mentions ethics committees that ensure compliance with ethical standards by healthcare workers. Specialists are well aware that this can result in additional bureaucratic overload, which can't be effectively confronted yet in real practice of genomic research regulation and use of

genetic technologies [1]. However, the positive experience of ethics committees in modern Russian medicine and science shouldn't be underestimated [2].

Mokhov A. A. justly observes that Federal Law as of 23 August 1996 No. 127-FZ 'Concerning Science and State Scientific and Technical Policy' doesn't have any mention of ethics in the field of scientific research. At that time, it seemed that the scientific society coped quite well with similar issues within existing scientific traditions and research practices. Indeed, scientific expertise organization has always been subjected to regulation by reviewers, opponents, scientific councils, scientific advisors, and departments in universities and research institutes. An ethical aspect assessing the prevalence of the topic or scientific novelty of the obtained results was present, if any, while discussing rather the means selected by a researcher to achieve the purposes than the purposes proper.

Doctors and legal scholars who come across ethical issues intuitively understand that it is impossible to appeal to any moral teaching or ethical theory while formulating the principles of bioethics. In other words, the knowledge of bioethics doesn't mean that general ethics penetrates into various spheres of social experience and respective cognitive practices, whether it be politics, economics, medicine or law. The subordination model of post-Soviet theory of cognition, where knowledge circulates within the philosophical, general and specific scientific levels, is first substituted by the coordination model and then disintegrates. The principles of bioethics are frequently interpreted by lawyers as a result of generalizing long-term generation experience or as legal practices but not as a product of paper-based philosophical considerations or religious revelations [3].

A point of view, in accordance with which bioethics doesn't originate from general ethics, is widely supported by philosophers. Gusseynov A. A. states that 'the issue of scientific and practical status of certain types of applied ethics can't find a unique solution for now. They don't obviously constitute parts or sections of ethics as science of morality, they belong to respective special areas of knowledge (biology and medicine for biomedical ethics, science studies for science ethics, etc.) to the same or an even a greater extent [4]. The issue about the mode of bioethical knowledge is far from being idle. The morality that substituted moral standards and simple copying of adults' behavior had existed as instructions, lectures and speculations from the very beginning. Tradition-supported authority is essential here. In case of Christian ethics (and any other religious morality), it is about the authority of the Holy Scripture and Holy Tradition, texts and their interpretation. But, eventually, there appeared quite many ethical theories, and their interpretations went beyond all the possible boundaries. That is why the question concerning how ethics can exist in the post-metaphysical epoch has turned into a pressing challenge of the XX century. Should it be based on certain metaphysics or religious doctrine just like it was before? Or is it formed by therapeutic and research practices just like in case with biomedical ethics, and the values of humanity are enough to determine the principles? One of the most pressing current issues is to organize legal and ethical expertise in the sphere of genetic research.

Mokhov AA notes that legal expertise has been quite common within the last two decades, irrespective of the fact whether an employer is represented by business, regulatory and administrative authorities, investigation authorities, courts, etc., whereas ethical expertise in the field of biomedical ethics is not yet significantly widespread and poorly codified. According to Mokhov A. A., 'though the issue about the ethical expertise with various variations (bioethical, humanitarian, social and ethical, etc.) applicable to innovations, healthcare and genomics is being discussed in the professional community, the issue about the legal expertise is not. However, ethics expertise can't consume legal ones, especially since there can be a conflict between ethical and legal standards in certain cases, thus requiring a complex approach to solving complicated ethical, legal and other issues of modernity' [5].

Meanwhile, the declared issue has been discussed in foreign literature as well. Moore A and Donnelly A believe that ethics committees are currently required to accomplish two tasks. They examine, first, whether research projects comply with the acting legislation (code-consistency) and, second, whether they are acceptable from the ethical point of view (ethics-consistency) [6]. The authors assert that the abovementioned tasks cannot be fulfilled by the same institution because these are different tasks both from the practical point of view, and considering the principles of their operation. In short, Moore A and Donnelly A believe as follows: the issue about the compliance of the considered projects to the legislation occurs due to legal uncertainty. The reason for it consists in quality of the laws proper, and wording of the laws and their gap with practice enquiries, in particular. The project compliance with ethical standards, when experts should focus on correspondence to bioethical principles but not legal standards, is quite another issue. Although codified law should not contradict to ethical standards and principles, the arising situations of legal uncertainty are solved in practice using the means and methods of the law itself due to unclear wording of the law in the field of biomedicine and are not different from other cases solved under conditions of legal uncertainty. At the same time, addressing to ethical arguments while attempting to resolve legal conflicts can destroy the law.

The ethical expertise appealing to the laws won't be considered as satisfactory as well. Moore A and Donnelly A state that 'thinking based on ethical consistency will have a tendency to combine the issue of which factors need to be taken into account during consideration with the issue of which problems are ethical. Emphasis will usually be placed on question whether legality of the suggested activity and scientific quality of the suggestion constitute ethical issues. It is difficult to provide principal answers to the questions, unless somebody appeals to any disputable and reasonably rejected ethical concept, rejecting other similar concepts' [7].

Subsequently, Moore A and Donnelly A mention that according to Aristotle and Mill, ethics encompasses regulatory and justifying speculations in the field of a practical action. At the same time, they state that Kant separates ethics from law and grants the sphere of ethics with limited jurisdiction considering it as a special but incomplete subset of a wider regulative set.

Thus, there occurs an issue of choice between different ethical theories, which obviously should not be a task of any ethics committee or supervisory board. The thought is expressed by Holm S who enters into polemics with Moore A and Donnelly A on the pages of the same edition. According to Holm S, 'research ethics committees do not represent philosophical seminars; they are not intended to develop research projects that could be optimal from an ethical point of view. They have to ensure that the research is ethically acceptable. It means that they need to authorize a deviation

from the law, if the law results in the outcome which is ethically unacceptable' [8].

Holm S. believes that Moore A and Donnelly A are mistaken thinking that ethics committees have to search for an ethically ideal way, whereas in reality, their function is to determine ethically unacceptable, but legally allowed actions within research projects. In other words, ethics committees can influence the law without being a separate source of it. Here it is better to consider the opinion of a reputable Russian specialist in the field of bioethics and medical law. According to Sedova NN, 'being a source of law, bioethics is different from morality, in general, and ethics, in particular. It rather requires legal formalization of its principles being closer to positive law regarding the content and mechanism of standards-compliant regulation as compared with other areas of ethics. Moreover, bioethics is a unity of theoretical and practical constituents, whereas ethics and morality are quite distinct as theory and practice' [9]. Moreover, bioethics can be included both into the structure and the content of law, this being both a soft, and a hard instrument [10].

In the context of the above, Nowotny H and Testa G hold a very curious opinion. They believe that bioethics is not related neither to law, nor to morality, without denying its connection with both of them. They see bioethics as a separate social regulator of a new generation. According to the authors, bioethics is a technology of humanitarian standardization acting as a central instrument of management that can balance 'the maximal possible specter of frequently mutually exclusive interests of a growing number of actors', manage the occurring interdependencies and develop administrative and legal policy in this sphere. Bioethics is considered by the authors as one of three social technologies of humanitarian standardization required to create complex sociotechnical system. Two other systems such as law and governance are not separated from each other and from bioethics, but form a complex sociotechnical complex.

Nowotny H and Testa G see bioethics as a means of building a new society and a means of restructuring its social institutions and values. According to them, 'the purpose is to develop the standards that allow to change and rebuild the forms of life. Thus, a deeper convergence of a molecular age is detected. Human technologies of a certain social maturity are close to biology which is open to setting social goals, accepting legal and ethical restrictions, taken into account from the very beginning, and includes them into its design. The common feature is that both of them represent complex systems that must be decomposed and reassembled again' [11].

A similar point of view is made by other authors. They note that there are rare examples of successful international regulation of genetic research based on ethical standards and principles of biomedicine. They believe that the appeals to bioethics increasingly remind of the so-called public involvement. 'The stereotype of bureaucratic ethical compliance with the rules no longer corresponds to the purpose in the world of CRISPR twins, synthetic neurons and self-driving cars. Bioethics does not rely on philosophical ideas any longer. Instead, it acts as a dashboard of pragmatic tools, and is managed by experts to the lesser extent' [12]. Politicians, journalists and social activists increasingly act as alternative bioethics experts, displacing specialists with respective advanced degrees and scientific publications.

In an interview, a French journalist asked Heidegger M whether he is ready to write 'Ethics' that could be interpreted as a doctrine of action in accordance with the tradition. 'Ethics?' asked the German philosopher. 'Who can afford this today and on behalf of which authority can this be suggested to the world?' [13]. It is natural that the words of the man who produced a rapidly increased intellectual and spiritual influence on the minds of his contemporaries, flirted with national socialism and paid for that by being banned from teaching could be associated with personal circumstances. The dispute about humanism entered by Heidegger with Sartre can also be explained by personal circumstances. Although more than half of a century has now elapsed, it is still a question today whether ethics can be appealed to as a source of knowledge or as a basis for judgement. Who has a right to speak on behalf and at the request of ethics? Is this right supported by the presence of some publications, influence in the scientific community or good attitude of the reading public? Or should evidence of lifestyle of someone who pretends to be an expert be exploited with his moral character and professional reputation being flawless? These questions make other ones recede into the background: which ethical doctrine must be followed by an expert and which values must be shared by him? To answer the question, it is necessary to remember that principles of bioethical declarations and biomedical conventions, that actually underlie the international biolaw, originate from philosophical seminars, literature, and other similar experience, which expands and specifies the ideas of human nature, dignity and rights.

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# LEGAL AND ETHICAL ISSUES OF ESTABLISHING THE BOUNDARIES OF INFORMED CONSENT

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The article deals with legal and ethical issues of establishing the boundaries of informed consent as a basic procedure being an integral part of medical practice, biomedical and clinical human research, and a broad list of medical procedures. A comparative analysis was based on examination of the best global models of informed consent. In the future, their implementation into the Russian legislative and regulatory compliance practices is suggested. The research uses the following methods: analysis and synthesis, analogy, method of legal modelling, and method of comparative legal research. Some conclusions were made about the reception of certain legal issues considering such factors as legal mental structure, level of legal culture, etc. In this article, the following aspects are highlighted: requirement for information disclosure, requirement to understand the relationship, a researcher's liability to enhance qualifications, a patient's responsibility, and the issue about an informed consent form.

**Keywords:** voluntary informed consent, boundaries, legal and ethical issues, legislation

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# ПРАВОВЫЕ И ЭТИЧЕСКИЕ ПРОБЛЕМЫ УСТАНОВЛЕНИЯ ГРАНИЦ ИНФОРМИРОВАННОГО СОГЛАСИЯ

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В статье рассматриваются правовые и этические проблемы установления границ информированного согласия как базовой процедуры, являющейся неотъемлемой частью медицинской практики, биомедицинских и клинических исследований с участием человека, а также широкого перечня медицинских процедур. Сравнительный анализ проведен на основе изучения лучших мировых моделей информированного согласия. В перспективе предполагается их внедрение в отечественную законодательную и правоприменительную практику. В исследовании использованы следующие методы: анализ и синтез, аналогия, метод правового моделирования, сравнительно-правовой метод. Сделан ряд выводов о рецепции некоторых правовых положений с учетом таких факторов, как правовой менталитет, уровень правовой культуры населения и пр. В статье освещены следующие вопросы: требование о раскрытии информации и требование о понимании их соотношения, обязанность исследователя совершенствовать свой профессиональный опыт, обязанности пациента, вопрос о форме информированного согласия.

**Ключевые слова:** добровольное информированное согласие, границы, правовые и этические проблемы, законодательство

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While obtaining voluntary informed consent, one of the most important issues includes establishing the boundaries of such consent — the data, situations and circumstances not covered by it or the situations that exclude obtaining such consent. It should be mentioned that the limitations are normally classified into legal and ethical ones. Ethical requirements are the most complex ones to be complied with. They are currently the least developed in the Russian legal practice. However, legal support of the issue in Russia leaves much to be desired as well.

It would thus be logical to call upon foreign expertise. But to do this, it is necessary to take into account typical features of the Russian legal regulation, legal mental structure and conservative strategy adhered by Russia with regard to biotechnology implementation, reception of law and adaptation of legislation due to accelerated development of innovative technologies in medicine. Note that legal regulation of the mentioned issues abroad depends on the established system of national and international legal instruments.

Moreover, defining the term 'informed consent' and its practical implementation are significantly different due to two main approaches:

a) This is an instrument with all required data about a patient and data for information such as adverse effects, contraindications or concomitant diseases a doctor must be informed of prior to therapy;
b) This a doctor-patient communication process when the entire necessary information and preliminary consultation are obtained, alternative treatment options are selected,

risks and advantages are assessed, etc. and which finally produces an influence on whether a patient's/participant's informed consent is provided or not.

## MATERIALS AND METHODS

Certain universal scientific research methods were used throughout the study. They included analysis and synthesis to find similarities and differences regarding the way the term and boundaries of the informed consent are comprehended; reflecting the abovementioned issues from the standpoint of medical ethics, and differences in legal regulation based on social, economic and mental factors; ways to improve the informed consent form, and development of consent typology depending on the type and purposes of treatment/medical intervention.

The need for using the method of legal modelling is implied from the above. The use of two private scientific methods — technically legal and hermeneutic methods — is absolutely essential as they enable complex estimation of the set issue legal constituent. During the research, the axiological approach was utilized, as three sciences — ethics, medicine and law — share their interests in the issue.

Nevertheless, the method of comparative legal research is the basic method used to study the informed consent institute abroad.

## RESEARCH METHODS

### Information disclosure: main approaches to fulfilling the requirement

In accordance with the standard approach, the requirement for information disclosure is similar to that of how a patient/client comprehends the information [1]. In particular, this position is reflected in basic international documents on research ethics. Based on article 1 of the Nuremberg Code,' a person who provides consent should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision' [2].

The Declaration of Helsinki states as follows with the regard to the procedure of data disclosure: 'In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and post-study health outcomes' [3]. Particular attention should be paid to the way the information is presented, as unlike young people, elderly usually require more detailed, simple, slow and clear explanations.

The Guideline of the Council for International Organizations of Medical Sciences (CIOMS) [4] contains 26 requirements for obtaining informed consent and 9 other specific requirements for the contents of the document. As far as information goes, it is stated as follows: 'Researchers should apply real-world data to transfer information and ensure its comprehension'.

With respect to the national legislation, the Belmont Report should be consulted. It provides that 'researchers have the responsibility to accurately establish the adequate data perception by a subject' [5].

The term 'adequate' is thus determined in every particular case. It is expected, however, that a subject has a certain level of comprehension. Possible risks can include the most common and serious consequences occurring during or after the research. Moreover, according to article 26 of the Declaration of Helsinki, 'the potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal' [6].

The explanatory work should always precede giving informed consent. In its content, the consent should correspond to the explanation. The 'concept' [7] restores the balance in doctor-patient relationship with simultaneous provision of connection between them: a doctor concentrates on treatment being free to take decisions, whereas a patient remains a master of his own body and health and can refuse from being treated by the doctor at any time.

It could not be established without a doubt that in Russian legal reality, informed consent is an integral legal concept because according to the author, the term primarily means compulsory compliance with the requirements. The requirements do not constitute a concept but serve as elements of obtaining consent and ensure its acceptability for subsequent studies. It is the lack of a clear single concept as an integrity of a doctor's — and especially of a patient'- rights and responsibilities and mutual responsibility that gives birth to the mentioned ethical and legal dilemmas.

Unfortunately, the Russian legal literature fails giving due attention to explanation as the central element of informed consent. Thus, it is appropriate to recall upon the experience of other countries.

According to another approach, requirements for information disclosure and comprehension have principally different etiologies describing the cases when obtaining consent can be declared null and void [8].

The primary aim of information disclosure is not to reach an understanding, but to avoid illegitimate control. For this, a subject requesting consent should share all available information which is associated with the consent-related decision by the subject and which is reasonably expected to be gained by the subject providing the consent [9].

The requirement for comprehension is based on conditions for successful oral consent. For the consent to be successful, a subject who gives the consent should understand:

1) that he/she provides the consent;
2) how to use the right to provide or withdraw the consent;
3) what exactly he/she gives the consent for [10].

### Requirement for comprehension: various opinions

According to the point of view about the subjective interests, the prerequisite of valid consent is that a subject who gives the consent comprehends all true (valid) suggestions about the study associated with the subject's interests. For instance, a potential participant must be aware of serious potential side effects of medications, because the side effects are related to compliance with and protection of the interests [11]. There are some illustrative examples that show the need of compliance with this requirement.

The first case considers an 18-year-old patient with mild ornithine transcarbamylase (OTC) deficiency, a rare hepatic disease, controlled with medicines and strict diet [12].

According to the patient's father, the patient provided a voluntary consent to participate in the innovative federal study of gene therapy because he was informed of low risks. However, researchers were aware of the fact that large doses of the gene medicine were toxic for animals. Cerebral death occurred four days after the injection. The researchers stopped the study. An initiated investigation resulted in governmental sanctions and judicial proceedings. During the civil trial, the plaintiffs claimed

that a lack of informed consent associated with the lack of data about previous unfavorable animal experiments and undisclosed direct financial incentives of the leading researcher facilitated out-of-court dispute resolution [13].

Quite frequent cases of children's compulsory vaccination by parents who rely on the doctor's experience and who are not interested in possible adverse effects are even more indicative. Data on adverse events from vaccination are available on the website of the Ministry of Health of the Russian Federation in small print. It is stated there that the percentage of adverse effects is small but they are rather serious and can even result in autism. Thus, the text should be mandatory reading. This is useful to determine whether subjects have sufficient knowledge not to refuse from their rights, but to make an informed decision about the participation. The more we are aware of what is raising difficulties in real participants, the better we are prepared for developing the process of obtaining consent for future participants.

**Responsibility to have a professional experience**

Researchers fail to perform another professional duty: responsibility to acquire and support the experience in their field of specialization. Just as a doctor has to work to keep up on medical affairs that are relevant to the patients, so a researcher needs to be aware of the latest achievements in his field of research. This is essential both for research participants, and for the quality of scientific results. Though the fact has hardly been mentioned, it is still a distinctive feature of good researchers [14].

Informed consent forms are frequently of a similar structure. They are stuffed with complex legal wording and institutional forms of protection, and commonly have several pages of complicated terms and explanations in small print. Many people sign these forms without going into details [15].

**Responsibility of a patient posed by informed consent**

There exist at least four rationales that make a patient much more responsible for implementation of the tasks: an epistemic, a deontological and two conceptual ones.

*The epistemic rationale* is based on two simple observations. They state that many changes in the way of life desirable to promote health are rather difficult to be implemented in reality and that doctors sometimes are not aware of how they are difficult for a certain patient.

*The deontological rationale* is directly based on the epistemic one. Responsibility towards the truth is mentioned rather frequently. Violation of this rationale is considered especially serious when a person is blamed for something he/she didn't do. As a rule, doctors don't know whether patients made every effort to, say, decrease their weight. The uncertainty is a sufficient rationale not to blame such patients for what they haven't done.

The first rationale relates to an ability of patients to change an unhealthy way of life. There are reasons to believe that chances of success are higher if patients set a goal and if they are encouraged to believe in their success [16]. So, if a doctor places responsibility for performing (a task) on a patient and lays emphasis on possible achievement of success, a positive effect can be expected.

The second rationale is about direct relationship between liability for fault and mental condition of a patient. There is some evidence that patients suffer when they are told that they are responsible for the existing disease. Other researches confirm that patients who blame themselves for the disease and believe that it is developed because of their drug-associated behavior have an increased risk of negative consequences for mental health such as depression [17]. In conclusion, it should be noted that people's sufferings can be strengthened by making them believe that it is all their fault. Obviously, it is an important reason not no transfer the messages [18].

Specific proposals aimed at a patient's better responsibility include agreements where a patient agrees with certain conditions of doctor-patient relationships such as a timely visit to a doctor, taking prescribed medications, clearance of arising issues and informing a doctor of the noted symptoms. Some hospitals issue the lists when drawing up documents for inpatients.

The American Medical Association has issued a detailed list of a patient's obligations including the ones to take preventive health promoting measures [19]. Standard suggested formulations state as follows: 'to provide the best possible case' or 'implement the purposes of taking care about your health'. There is no mention (at least printed one) of punishments or consequences faced if a patient fails to fulfill the obligations.

The status of similar lists and agreements is unclear. Unlike it happens after signing the informed consent form, violation of a patient's promise to take the prescribed medications and follow the recommended diet doesn't represent any moral or legal basis for treatment refusal or discharge from hospital. What if such contracts acquire the same moral and legal status as an informed consent form? Non-fulfillment of a doctor's responsibilities implies tangible consequences. The doctor can be reprimanded, deprived of a license, dismissed or subjected to prosecution. Even if none of this happens, the doctor can lose patients' trust because of bad feedback.

**Informed consent form**

It is not specified in legislation of many countries, including the Russian Federation [20] and the Federal Republic of Germany. In Germany, they basically use a written form while performing a surgery. There is differentiation between an abstract form (consent for a certain intervention with blank space where the risks are described by the doctor) and a specific brochure that contains non-fiction text about this intervention. Besides, the doctor interviews the patient who can ask questions.

In Poland, there exist two forms of consent in medical law: a standard or given in a written form. The first one means a verbal or implied consent which gives rise to no doubts. The written form must be given in a positive and preliminary way. The law of Poland regulates situations, in which minors, incapable or other persons are involved; it also differentiates between the types of medical interventions that require compulsory provision of consent in writing [21].

In spite of thorough legal discussion, the concept of explanation and consent is limited by the humanistic principle in which a doctor's commandment of causing no harm should be taken into account during an explanation of a fatal diagnosis. In some cases, it means that the diagnoses should be willfully concealed.

There are *three types* of such situations:

- mental contraindications;
- possible increase of risk, for instance, in case of a heart disease, understanding the data can result in infarction;
- endangering other persons, for instance, in case of a mental disease, diagnosis reporting can result in increased aggression against close relatives.

CONCLUSIONS

To sum up, it should be noted that in spite of abundance of legal models that consolidate different aspects of informed consent, none of them was considered by a Russian legislator while legislation improvement. This is a mere omission. Nevertheless, there exist ways to implement positive and informative foreign experience into the Russian system of legislation.

First and foremost, this includes establishment of a general guideline for effective support of informed consent obtaining. In Russia, attempts were made — to no avail yet — to create the ethical code. Moreover, it was supposed to be a single unified document consolidating the ethical issues of clinical research, personalized medicine, genetic research, genome registration, passporting and other similar issues that would definitely arise due to development of technologies and new trends in research. But this is not sufficient and the document would probably be hard to implement. The reason can include a large scope of proposals and lack of real ability for their implementation. It would be more effective to create separate brief and broad documents for the most complex and challenging fixed points — informed consent being one of them — with their subsequent implementation into medical practice. In this case, a necessity in formulating numerous blanket and reference rules ceases to exist. In the documents, it's required to consider the basic essential principles created in the image of the Belmont Report and key aspects of fulfilling the requirements, develop a typology of consent forms depending on the area of their application. Moreover, it is necessary to lay down the rights and obligations of every party in detail. In our opinion, the documents will improve the acting federal laws and legislative instruments in a more simplified and rapid way.

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# ABOUT SOME ISSUES OF LEGAL REGULATION OF THE STATUS OF PARTICIPANTS INVOLVED IN GENOMIC RESEARCH

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Continuous development of social relations implies the need in constant improvement of primarily legislative regulation so that it could adapt to the current realities in the society and country. This assumption is true both with regard to the legal regulation of the status given to participants of genomic research, as this relatively new area of social relations embraces both public, and private interests. In this respect, legal regulation should consider certain principles such as the balance of public and private interests, protection of human rights and freedoms, protection of sensitive data by the law, protection of the national interests, etc. Nevertheless, normative legal regulation of the status of genomic research participants in the Russian Federation is not complex in nature yet. Thus, it fails to result in development of this area of social relations and ensuring the rights, freedoms and legitimate interests of the mentioned persons. It is necessary to settle the issue about the boundaries of the allowed behavior, rights, obligations, guarantees and liability of genetic research participants. It seems to be appropriate to develop a complex federal law about the legal status of genetic research participants in the Russian Federation. A general approach to arranging complex legal regulation in this field consists in systematization of the existing legal regulation considering legislative regulatory activity of the discovered issues in the field of using genetic technologies and conducting genome research. During the regulatory control, it is necessary to reflect common moral and ethical principles and standards of medical and genetic research.

**Keywords**: human genome, genomic research, legal status, legal regulation, patients, research scientists

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# О НЕКОТОРЫХ ВОПРОСАХ ПРАВОВОГО РЕГУЛИРОВАНИЯ СТАТУСА УЧАСТНИКОВ ГЕНОМНЫХ ИССЛЕДОВАНИЙ

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Непрерывное развитие общественных отношений влечет за собой необходимость постоянного совершенствования, в первую очередь, законодательного регулирования, чтобы оно отвечало сложившимся в обществе и государстве реалиям. Данное утверждение является верным и в отношении правовой регламентации статуса участников геномных исследований, поскольку данная относительно новая сфера общественных отношений сочетает в себе как публичные, так и частные интересы. В этой связи правовое регулирование должно учитывать такие принципы, как баланс публичных и частных интересов, защита прав и свобод человека, защита охраняемой законом тайны, обеспечение национальных интересов государства и т. п. Однако до последнего момента нормативное правовое регулирование статуса участников генетических исследований в Российской Федерации не имеет комплексного характера, что не способствует развитию данной сферы общественных отношений, а также обеспечению прав, свобод и законных интересов отмеченных лиц. Необходимо посредством права решить вопрос о границах дозволенного поведения участников генетических исследований, их правах, обязанностях, гарантиях и ответственности. Представляется целесообразной разработка комплексного федерального закона о правовом статусе участников генетических исследований в Российской Федерации. Общий подход к выстраиванию полноценного правового регулирования в данной сфере видится в систематизации сложившегося правового регулирования с учетом необходимости законодательной регламентации выявленных проблем в сфере использования генетических технологий и проведения геномных исследований. Также при осуществлении такого нормативного регулирования должны получить отражение общепризнанные морально-этические принципы и нормы проведения медицинских, а также генетических исследований.

**Ключевые слова:** геном человека, геномные исследования, правовой статус, правовое регулирование, пациенты, ученые-исследователи

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Modern genomic research provides access to previously inaccessible areas of disease prevention and treatment, development of the latest methods of clinical diagnostics, family planning, crime fighting, etc.

Genomic research, however, directly touches upon fundamental human rights (human dignity, protection of privacy and health, etc.). So, observance of these rights needs particular attention. It is also necessary to develop the respective legal acts. This legal regulation should consider the values that are significant both for the society, and the country such as the balance of public and private interests, necessary development of Russian science, compliance with rights and freedoms of a person and a citizen, protection of legally guarded confidential data, etc.

Normative legal regulation of social relations in Russia can currently be of a fragmented nature, because it is ultimately about the issues of state genomic registration, gene engineering, and genomic (genetic and molecular) expertise.

In this connection, the issue about the balanced interests of different participants of genetic research and selection of an optimal model of legal regulation of these social relations might also be relevant. On the one hand, the rights, freedoms and interests of patients and their relatives must definitely be respected. On the other hand, excessive restrictive regulation

might significantly complicate and actually slow down development of the Russian genetic science, which is now inferior to that in other countries (USA, Great Britain, Germany, France, etc.) as it is.

Thus, a balanced option needs to be selected that would ensure both patients' rights and freedoms in accordance with international standards, and freedom of scientific activity. This can be done by reducing an unreasonably vast number of administrative barriers, just like they did it in the USA, a world leader in genetics.

A huge potential of using genomic research results makes it relevant to adopt the respective normative legal framework and state programs (Presidential Decree of the Russian Federation as of November 28, 2018 No. 680 'Concerning development of genetic technologies in the Russian Federation', Government Resolution of the Russian Federation as of April 22, 2019 No. 479 'Concerning approval of the Federal scientific and technological program of genetic technology development for 2019–2027', etc.)

Along with handling the issues of genetics innovative development and use of genetic research results in different economic sectors (agriculture, food supply, healthcare, etc.), there exists an objective need in legal regulation of the status of genetic research participants. This particularly concerns the legislative establishment of the boundaries of allowable behavior of genetic research participants, their rights and obligations, guarantees and responsibilities.

## RESEARCH RESULTS

It appears that genetic research participants can be subdivided into two groups.

I. Persons, whose genetic materials is used for the purpose of the genetic research.
   1. Patients are people who provide consent to use of their genetic material during genetic research.
   2. Persons having a genetic relationship with patients.

II. Subjects involved in organization or direct conduction of the genetic research.
   1. Organizations.
   2. Research scientists.
   3. Medical personnel.

The legal status (rights, obligations, guarantees and responsibility) of the mentioned participants of genetic research should be reflected in the respective legislative regulation, for instance, by way of adopting a separate federal law about the status of genomic research participants. In this respect, the Russian legislator should not only follow the widely accepted international standards of how medical — including genetic — research should be conducted, but also pay attention to the existing models that legally regulate the status of genetic research participants. A basic model should be selected while observing the constitutional values, and accepting the need to develop genetic research in Russia.

It must be noted that the legal status of patients as participants of any medical and scientific research is based on interrelated provisions of the Constitution of the Russian Federation as of 1993 and international rules (Convention for biological diversity as of June 5, 1992, Convention for the protection of human rights and fundamental freedoms as of November 4, 1950, Convention for the protection of human rights and dignity due to the use of biological and medical achievements: Convention on human rights and biomedicine as of April 4, 1997, etc.) [1].

The following provisions of the Constitution of the Russian Federation should be noted: the ultimate value of a person, his/her rights and freedoms (art. 2); equal rights, freedoms and responsibilities for all citizens (part 2, art. 6); protection of human health and labor by the state (part 2, art. 7); the principle of ideological diversity which means that it's impossible to pose restrictions or obligations on citizens depending on any ideology (part 1, art. 13); protection of human dignity by the state, prohibition of tortures, violence, other cruel, inhuman or degrading treatment or punishment, or being subjected to medical, scientific or other experiments without voluntary consent (art. 21), protection of privacy, personal and family confidential data, protection of honor and good name (part 1, art. 23); prohibition to collect, keep, use and distribute data about a person's private life without his/her consent (part 1, art. 24); warrant of judicial remedy of rights and freedoms (art. 46), etc.

The list of constitutional rights is open. This guarantees that it is impossible to deny or restrict other common rights and freedoms of a person and citizen.

Particular attention should be paid to part 2, art. 21 of the Constitution of the Russian Federation. It states that nobody can be exposed to medical, scientific or other research without voluntary consent. Human dignity is of subjectively legal and objectively legal nature. On the one hand, the country is prohibited to willfully infringe on an individual's autonomy; on the other hand, the country needs to create a system of justice excluding infringement on personal dignity on the part both of the country, and individuals.

In a number of its decisions (Decision as of Febr. 18, 2000 No. 3-П; Orders as of Jan. 29, 2009 No. 3-О-О, as of Sept. 29, 2011 No. 1063-О-О), the Constitutional Court of the Russian Federation noted that in accordance with some interrelated provisions of the Constitution of the Russian Federation (part 4, art. 29; part 1, art. 23; part 1, art. 24), it is prohibited to collect, keep, use and distribute the data associated with violation of constitutional human rights to privacy, private and family confidential information. In this regard, it needs to be considered that genomic data completely conforms to the features of personal data established by the federal legislation on personal data. Thus, we need just to define an optimal legal regimen of personal data that should be used in relation to genomic information about citizens.

Moreover, in some decisions of the Constitutional Court of the Russian Federation it has also been noted that as human rights (part 3, art. 17 and part 3, art. 55) can be limited based on the federal law of certain constitutional value protection, realization of the constitutional right to the information that affects the private life of other persons should be regulated in the manner established by the law; the Constitution of Russia accepts that a special legal regimen -including the regimen of restricting free access to the third parties — can be used with regard to some data.

We assume that people with genetic relation to the patients should be considered as participants of genetic research with a special status. As relatives are genetically related to patients, genetic research and obtaining the respective information will impact their rights and legal interests. This provision is based on part 3, art. 17 of the Constitution of the Russian Federation stating that exercising human and civil rights and freedoms should not violate the rights and freedoms of other people. Accordingly, when exercising the rights and freedoms of his own, a citizen (patient) must not violate the rights and freedoms of other people or genetic relatives, in particular (for instance, a right to privacy, personal and family confidential data).

Ensuring the compliance with the regimen of personal data of the persons whose genetic material is used for genetic research remains the cornerstone of the issue of legal regulation. It is assumed that a legislator needs to consider an increased level of personal genetic data legal protection. There are several reasons for that.

First, genetic data about the patient directly influences the rights of his/her genetic relatives, including the minor ones, as it carries certain information about their health, mental condition, typical behavior [2: 186–188].

Second, genetic material analysis enables effective identification of a person (and his/her genetic relatives) which is actively being used to combat criminal activities [3].

Third, the issue of creating unauthorized genetic data banks compiled by way of uncontrolled collection of their genetic material (without their voluntary consent) is getting more urgent these days. For instance, the results of citizens' genetic research are of major interest for employers and insurance companies, as it can provide data about possible human genetic predisposition, including predisposition to a certain disease, and cognitive capacities [4: 69–70].

Thus, some companies can already use these data upon recruitment, promotion, termination or when distributing tasks and solving insurance issues.

At the same time, genetic data can't be utilized to precisely predict a person's future, as 'the increase of an individual risk by two or five times even in case of high population risk (for instance, 1/1000) doesn't mean that the subject will be affected by that disease. Consequently, even under GWAS conditions, it can now be only determined whether a person relates to the group of high risk for a multifactorial disease; but it is not possible to provide sound prognosis about implementation of this risk for a certain individual' [5: 83]. In this respect, a person with no diseases can be a victim of discrimination on genetic basis just based on a probability of their occurrence, which is unacceptable in the modern legal democratic country.

Fourth, genetic information is a specific type of personal data. It requires improved measures of state protection because genetic data (unlike biometric data, residential address) identifies and characterizes a wide range of persons who have a genetic relationship with the patient, including subsequent generations. Thus, the data will to some extent be related to the patient's descendants and genetic relatives. That's why, theoretically speaking, it will be indefinite in nature.

The Russian legislator should, tailored to the particular situation, set forth by legal acts and guarantee compliance with the rules of conducting genetic research and using the obtained results, that are widely accepted by the leading countries on the scientific and legislative levels, genetic data confidentiality and prohibition of its transfer to the third persons. In addition to that, it is also necessary to obtain consent of close (and far) relatives with genetic relationship to the patient to authorize the research and use the obtained results for legitimate purposes.

Regulation of the legal status of the subjects who conduct genetic research should also include such elements as rights, obligations, guarantees and responsibility. Considering a complex nature of these social relations and particular value of genetic data about a human being, the principal activities of legislative regulation of the subjects' activity should be as follows:

1) ensuring legitimacy and transparency of the noted research activity;
2) establishing the corresponding obligations, and mechanisms of holding legally responsible to observe patients' rights and freedoms;
3) enhancing development of genetics, state support of research aimed at improvement of citizens' health and protection of national interests.

There is no legal certainty in the issue of legislative regulation of the nature, methods and standards of genetic research in the country, prevention and elimination of genetic discrimination. It can be asserted that Russia is on the path of building a complex model of legal regulation of carrying out genetic research.

The acting Russian regulatory acts and judicial practice neither establish the content of human rights in the area of genomic research, nor state specific legal guarantees; the human genome is not considered as a legal element to protect health and provide medical aid.

It is possible to agree that the principal modern threats in the sphere of genomic data handling faced by Russia until now can include cost-intensive nature, unauthorized access, errors, massive screenings, irresponsible collection and irresponsible storage of genomic data [6: 136]. Given that determining position of one gene in a human genome enables errorless identification of the only person out of 10 billion others, conducting genomic research sets certain tasks in the sphere of protection of personal data, private life, medical, family and other law-protected confidentiality [7: 183].

Another issue is to establish liability for committing offences in the regarded area of social relations. On the one hand, causing harm to patients' health by genome editing or gene therapy is not permitted and must include the use of the corresponding measures of legal (disciplinary, administrative, criminal, civil) liability to those guilty. On the other hand, it is necessary to consider the circumstances in every particular case and bear in mind that conducting genetic research is difficult. Though medical mistakes are almost inevitable when working at any innovative projects in the sphere of genetic technologies, legal regulation at various levels should ensure development of open, clear and substantiated rules of behavior for genetic research participants.

Moreover, after genomic research has been conducted, the issue of legal protection and support of the genomic information obtained becomes relevant. Analysis of the acting criminal and administrative legislation of the Russian Federation and judicial practice allows for the conclusion that using legal liability in this area is highly problematic as there are no specific standards devoted to genomic data protection, human genome editing, prohibition to transfer genomic data to the third parties, etc. Meanwhile, the administrative regulation addresses only responsibility for violation when using genetically modified organisms (GMO) or GMO-based products [8: 65–66].

## DISCUSSION RESULTS

It is necessary to accept that distance between specialists engaged in genetic and genomic research does not promote development of unified ethical requirements [9: 56]. Well-established requirements in the area of genetic consultation while revealing orphan (rare) diseases are incompatible with a complex set of ethical issues that arise in genomic counselling, during which the patient's and his/her family's interests regarding both protection of the person's general rights and interpretation of personal data obtained during the research are combined [9: 57].

It seems that the discussions that arise in science in this regard relate to the researcher's behavior algorithms that are acceptable in professional ethics. Due to this reason, ethical requirements must be developed not just by professional communities of genetic scientists, but also by industry medical associations (for instance, professional communities of oncologists including medical clinical genetic scientists) [10].

Moreover, it is suggested in the Russian legal literature that a qualitatively new model of genomic research self-regulation should be used. However, it's about the experimental experience [11]. Thus, we need to pay attention to basic legal regulation.

The acting Federal Law as of December 1, 2007 No. 315-FZ 'Concerning self-regulatory organizations' states that self-regulation is an independent and initiative activity implemented by the subjects of entrepreneurial or professional activity and that its content consists of development and establishing standards and rules of the mentioned activity and control over compliance with the requirements of the mentioned standards and rules. In this case, two forms of self-regulation are possible:

- self-regulated organizations that unite the subjects of entrepreneurial activity considering the unity of the sector that produces goods (works, services) or market of the produced goods (works, services);
- self-regulated organizations that unite the subjects of professional activity of a certain type [12].

Modern medicine is based on epidemiologic research results, whereas clinical practice rests on the principle of Evidence Based Medicine. The both approaches mean that probability estimates and risk estimates (results of genome deciphering require that a specialist could determine and assess the possible risk, whereas a consumer needs to perceive the risk adequately and take a willful decision) are being utilized [13]. This model of interrelations must be reflected in the legislation of the Russian Federation with subsequent specialization at the sublegislative legal level.

In this regard, in Russian legal literature it is correctly noted that the issues associated with the legal sphere must be solved within self-regulated organizations uniting the subjects of professional activity (professional associations):

- informed consent to conduction of genetic research and protection of sensitive data obtained as a result of the research;
- participation of self-regulated associations of medical genetic scientists in development of national quality standards of genetic research, requirements to medical and non-medical organizations, and employees who provide the services;
- legalizing the status of a person who provides consultations services in the sphere of genetic research and accompanying spheres associated with determining the treatment strategy of genetic diseases and use of assisted reproductive technologies (genetic consultants);
- the issues of compliance with international and national ethical requirements to conduction of the research [14: 36].

However, the noted pressing issues have not been properly regulated by the Russian legislation until now.

Thus, the issue about the balance of interests of various participants of genetic research and selection of an optimal model that legally regulates the noted social relations is still one of the major issues [15]. On the one hand, the rights, freedoms and interests of the patients and their relatives need to be followed. On the other hand, excessive restrictive regulation can significantly complicate and actually slow down development of the Russian genetic science, which can currently be inferior to the countries that lead in this sphere (USA, Great Britain, Germany, France, etc.).

## CONCLUSIONS

Based on the abovementioned facts, the following conclusions can be made:

1. Nowadays Russia lacks a complex legislation regulating the status of genomic research participants, though the sphere is perspective and very important for the society and country (the fact being reflected not just in scientific literature, but also in bylaws and instruments of strategic planning). It could be associated with a complex selection of an optimal model of legal regulation that would sufficiently protect human rights and freedoms (patients, donors, relatives), promote development of science and respective sphere of provision of medical services and serve the national (public) interests.
   In this context of 'legal vacuum', the basic rule for doctors, scientific researchers and medical workers who participate in this research consists in the no-harm rule. This provision should also promote urgent and complete information of a patient of any risks of a medical intervention.
2. It is assumed that scientists and experts can determine the boundary of allowable behavior as far as genomic research is concerned by developing the respective documents. In this regard, it should be noted that apart from legislative regulation of the considered area of social relations, it is self-regulation of genetic research — regulation by organizations that conduct genetic research, their associations, and respective professional and scientific communities (by means of local acts, agreements, memoranda, professional standards, ethical codes), relations in the sphere of the organization, conduction and using the results of genetic research — which is essential in the world practice. Their analysis will enable to understand the general condition of self-regulation in this sphere and develop an optimal model of self-regulation for these organizations and subsequent legislative regulation of genetic research in the Russian Federation.
   However, the general regulative potential of bylaws of Russian companies that conduct genetic research is not currently fulfilled to a significant extent. This corresponds to general fragmentary nature of the legislative basis and compliance practice. The institution of genetic research self-regulation is poorly developed in Russia. The fact is being supported by analysis of data about activity of the corresponding companies (both state, and non-state) from the web site (primarily, on the Internet). Published ethical codes about genetic research, standards of genomic research approved by genomic organizations, documents protecting the rights of patients who participate in genetic research, etc. are nearly non-existent.
3. Insufficient legislative regulation and self-regulation of genetic research in Russia can promote violation of patients' rights and freedoms with regard to ensuring security of genetic data, protection from voluntary gene editing, transfer of the obtained genetic material to the third persons without a patient's consent, etc. Apart from that, the situation will produce a negative effect on genetics (genetic research) reputation in the society, decreased trust of citizens in this science, securing a position about a great danger of genetics relating to violation of human rights in public opinion.
4. Within the purpose of intense development of genetic technologies that has been set earlier, the country should create necessary conditions, including those of legal nature, that could promote achievement of the set tasks. Legal regulation of the status of legal research participants and ensuring security of genetic data still belong to one of these tasks. Genetic data obtained during respective genetic research must be protected from any unauthorized use, whereas rights, obligations, guarantees and legitimate interests of genetic research participants should be regulated at the level of legislation, so that they could correspond to well-known international standards and advanced foreign practices.

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# PERSPECTIVES OF GENOME EDITING IN HUMANS: RISKS, PROBLEMS AND LEGAL REGULATION

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The article deals with aspects of legal regulation of human (somatic, germline, heritable) gene editing techniques. Principal risks and problems of implementing these techniques in clinical practice are mentioned. The experience of using the techniques of genome editing and recommendations of WHO 2022 are analyzed. Special attention is paid to conflicts of interests and conflicts of liabilities while creating the concept of legal regulation of genome editing in humans. The conclusions are drawn concerning the necessary disclosure of data about the conducted research and results obtained globally to create the principles and standards of legal regulation of genome editing in humans. In spite of the existing controversies between the scientific communities and countries, it is extremely important to promote an international dialogue, as human genome editing concerns everyone and future generations, variety of human community and safe life and health.

**Keywords**: human genome, CRISPR/Cas technologies, genetic editing, human embryo, human germline engineering, somatic editing

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# ПЕРСПЕКТИВЫ ИСПОЛЬЗОВАНИЯ ТЕХНОЛОГИЙ РЕДАКТИРОВАНИЯ ГЕНОМА ЧЕЛОВЕКА: РИСКИ, ПРОБЛЕМЫ, ПРАВОВОЕ РЕГУЛИРОВАНИЕ

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В статье рассмотрены аспекты правового регулирования применения технологий генетического редактирования генома человека (соматического, зародышевой линии, наследуемого). Указываются основные риски и проблемы процесса допуска данных технологий к применению их в клинической практике. Проанализирован опыт использования технологий генетического редактирования и рекомендации ВОЗ 2022 г. Особое внимание уделяется конфликтам интересов и конфликтам обязательств при формировании концепции правового регулирования генетического редактирования генома человека. Делаются выводы о необходимости раскрытия информации о проводимых научных исследованиях и полученных результатах на международном уровне для формирования принципов и норм правового регулирования генетического редактирования генома человека. Крайне важно, несмотря на имеющиеся противоречия между научными сообществами и странами, способствовать развитию международного диалога, поскольку генетическое редактирование генома человека касается каждого из нас и будущих поколений, многообразия человеческого социума и безопасности жизни и здоровья.

**Ключевые слова**: геном человека, технология CRISPR/Cas, генетическое редактирование, эмбрион человека, редактирование зародышевой линии человека, соматическое редактирование

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In 2022, the first international recommendations of the World Health Organization (WHO) were published regarding integration of human (somatic, germline and inherited) genome editing as a mode of treatment into the system of public healthcare considering the principles of safety, effectiveness and ethics. The WHO reports were formulated on the basis of biennium work participated by the hundreds of scientists, researchers, patients, representatives of various religious denominations, social organizations and indigenous people from around the globe.

According to WHO Director-General Tedros Adhanom Ghebreyesus [1], human genome editing can improve the ability to treat and cure diseases, but complete exposure can be achieved only when the technology is used for the benefit of people, but not to exacerbate the inequality between and inside the countries.

Potential advantages of genome editing in humans involve faster and more exact diagnostics, targeted treatment and prevention of genetic disturbances. Somatic gene therapy which includes modified DNA of a patient for treatment or curing of the disease is currently used for successful treatment of HIV, sickle cell disease and transthyretin amyloidosis. This method can significantly improve therapy of various types of cancer. However, there exist some risks associated with germline and heritable human genome editing that alter the genome of human embryos and are inherited by subsequent generations changing descendants' traits.

The published reports contain recommendations regarding management and surveillance over human genome editing in nine separate areas including registers of human genome editing, international studies, illegal, non-registered, non-ethical and unsafe trials, aspects of intellectual property, education, expansion of rights and possibilities in this area. The recommendations are based on system-level improvements required to form potential in all countries to ensure safe, effective and ethical use of human genome editing.

The reports also contain a new structure of management, which determines certain tools, scenarios, practical issues while implementing, regulating and monitoring the research in the area of human genome editing. Certain recommendations are suggested (for instance, conducting clinical trials of somatic human genome editing in sickle cell disease in the South Africa).

Somatic or epigenetic genome editing in human beings is used to improve sports results.

These new WHO reports represent a major step forward in the area of genome editing. As global studies go deeper into the human genome, it is necessary to mitigate the risks and use only the modes that remained positive from the scientific and practical point of view.

The leading experts in human genome editing based on CRISPR/Cas technologies, Nobel prize winners Jennifer Doudna and Emmanuelle Charpentier do not only specialize in human genome editing, but are also public defenders in the area of creating a legal framework in genome editing. Scientists create a necessary moral and ethical basis for legislation in gene engineering.

The CRISPR/Cas technology has altered the landscape of biomedical research and genome engineering as a more efficient, exact and widely used method of genome editing emerged with significant advantages over ZEN and TALEN alternative technologies.

Potential areas of using CRISPR/Cas technologies include genome editing to treat monogenetic diseases (cystic fibrosis), polygenetic and multifactorial diseases (Alzheimer dementia), reduced risk of polygenetic and multifactorial disorders (reduced underlying risk for breast and ovarian cancer).

The technical issues and risks that arise when the technology of human genome editing is used are of note. This results in debates about moratorium on clinical use of heritable human genome editing (editing of human germline and gametes, oocytes and germ cells).

The first risk or technical issue is represented by non-target editing, which is being a subject of many scientific studies [2, 3]. Second problem, genetic mosaicism, consists in the fact that while editing genome in a zygote or embryo at the early developmental stage there is a probability that some cells in the obtained mechanism won't be edited as desired. Two or more various genetic sets of cells can result in health issues [4]. Third, some genes that cause serious genetic disorders protect their carriers from infectious diseases (in sickle cell disease, inheritance of genes from the both parents contribute to occurrence of this disease in a child, however, inheritance of the gene from one parent will result in natural immunity to malaria) [5].

Another technical issue is current inability to select the genes that are suitable for editing with highest precision. As we still know little about human genes, genetic variants and interrelations between genes and environment, it can't be warranted that suitable genes for genetic editing will be selected.

These and other technical and ethical issues give birth to uncertainty about human gene editing and inhibition of legal regulation.

Nevertheless, perspectives of using this tool in heritable editing raise a number of complicated bioethical and legal issues. In 2018, the scandal surrounding He Jiankui, a biophysicist, made an attempt to solve the issues urgent [6, 7]. He was responsible for an experiment, in which a genetic mutation in human embryos was induced using CRISPR/Cas9 to contributing to resisting infection with HIV.

It is worth mentioned that he founded at least two companies: *Direct Genomics* engaged in developing a device to sequence single molecules (technology made by Stephen Quake and licensed by *Helicos Biosciences* [8]), and *Vienomics Biotech* in 2016, offering genome sequencing and screening for oncological patients and groups of risk. When he reported the experiment during the Second World Summit on Genome Editing in Hong Kong, he received a three-year sentence and was fined RMB 3 million (465 thousand US dollars).

The experiment resulted in resumed debates about legal and regulatory regulation of the studies associated with human genome editing and calling to impose moratorium on human germline engineering. Some experts were against the moratorium [9], others offered to introduce temporary moratorium on clinical studies to develop international framework and ethical and legal guidelines at the national level [10].

There are three objections with regard to this experiment: lack of transparency regarding scientific and organizational aspects of this issue; lack of medical necessity as alternative methods of conception of healthy offspring and not correct classification of the experiment as a mode of treatment are available; illegal experiment and ignoring biomedical study protocols.

Moreover, it is necessary to consider other disturbances of research medical and scientific ethics that occurred during this genetic editing and birth of the twins.

The informed consent form with 23 pages was written using plain technical language and contained no discussion of side effects or undesirable non-targeted genome exposure. A widely spread method of extracorporeal fertilization used with one partner being HIV-positive wasn't mentioned.

Editing was considered as a favorable alternative to treatment. The consent form wasn't approved by the Institutional Review Board where He Jiankui was a member. The scientist avoided expert assessment too, announcing the experimental results in a video hosted on youtube. com on November 25, 2018; neither the research work, not experimental results were presented. Thus, consequences are not clear until now. Moreover, it was reported that another couple participating in this experiment gave birth to the third child in 2020. The experiment was neither registered not approved by an independent Ethics Committee. Documents for Ethics Expertise were falsified to attract volunteers. The experiment was conducted at the expense of the scientist, which enabled to avoid control [11].

This experiment displays non-targeted consequences of genome editing: the edited gene plays a protective role in immune reactions against the West Nile virus found in Europe, Africa and North America, and the lack of it can result in a lethal outcome in influenza viral infections [12].

Another important aspect in this experiment that needs to be considered when legal standards are formed is the difference between 'treatment' and 'improved conditions of an organism'. Apart from resistance to HIV, experiment-edited gene can improve certain cognitive abilities (for instance, during the experiment, improved memory function was shown in rats and better restored process following strokes and craniocerebral traumas was found in humans [13]). Thus, medication therapy does not strictly fall into elimination or mitigation of the disease; it is rather about improvement of health that results in risk reduction.

The case is inseparably associated with CRISPR/Cas development and is a paradigmatic example of a scientist who was too interested in scientific reputation and had vested commercial interests not to evade the laws and bioethical standards.

That is why the experiment displayed an urgent need in legal regulation both at the international, and national level.

Searching for treatment and prevention of genetic disturbances with the help of germline editing should correspond to the principles of well-being. They are used to

relief or prevent human sufferings. The ethical principles were formulated prior to the epoch of human genome engineering (by Fletcher and Andersen in 1992) and triggered development of bioethics [14].

A variety of scientific, legal, ethical and administrative issues associated with human genome editing is being discussed now. Leading scientists often rely on introduction of moratorium regarding clinical studies of human germline engineering, but leave open a possibility to conduct fundamental studies [10]. The studies are considered as necessary scientific practice to analyze the risk and benefit relationship, which is an essential stage for a subsequent clinical study of clinical use of genome engineering technologies.

It is obvious that applying a global moratorium is impossible, as accessibility of CRISPR/Cas technologies doesn't allow to trace its use, for instance, in private companies or countries with no national laws and regulation regarding human genome engineering. From the philosophical point of view, there arise questions about the extent to which the moratorium is compatible with common values of scientific freedom and about the relevance of any actual obstacle to scientific progress, especially in such rapidly developing areas as genetics and biomedicine [15].

Discussing the clinical use of human genome engineering, we need to consider the aspect of determining exact criteria for clinical use. The issues are associated with using human embryonic stem cells and products of synthetic biology such as cellular models of embryos and embryoids. Considering possible embryo cloning *in vitro* aimed to obtain organs and tissues from stem cells, there was a question whether artificially and naturally created embryos can have an equal status. In the report of the Council of Europe as of June 19, 2003 'Protection of human embryos *in vitro*' [16], an interesting and highly relevant question was addressed (whether there is a difference between natural and synthetic embryos).

According to the reporters, an embryo created by way of transferring a somatic cell nucleus into an egg without a nucleus, just like with Dolly the sheep, can't be considered equal to the embryo obtained during fusion of an egg and a germ cell. That's why the status of the embryos differs irrespective of development potential. It means that the cloned embryo doesn't have the same rights as the natural embryo, even if it was obtained using the methods of assisted reproductive technologies. From a legal point of view, differentiation between various cellular substances and human embryos is of value for legal regulation of obtaining, storage, using, transferring and utilizing human embryos and other cellular substances of embryonic nature.

Human parthenotes should be differentiated from human embryos without giving them the status of legal protection; it is necessary to determine restrictive criteria without reference to totipotency and development potential to protect human embryos from commercial usage. It is important to consider not just development potential, but also the purpose of using embryos and other cellular substances. The criterion of cellular material origin includes fertilization, SCNT (somatic cloning by nucleus transfer into human somatic cells), parthenogenesis. The ultimate development purpose criterion includes birth or bringing to a certain stage of embryonal development.

Scientists and ethics committees of many countries are inclined not to use the human germline editing until the risks and advantages are sufficiently examined. It takes time to create the legal basis of editing chromosomal and mitochondrial genetic data. Slow public recognition of possible use of genetic editing is essential. For instance, genetic editing of human germline can be done while treating monogenetic disorders considering that the ratio of risk and benefit is currently being positive.

It should be noted that CRISPR/Cas technologies belong to a very valuable sector in the rapidly growing market of biotechnologies [17]. This complicates the debates and formation of single standards and principles. Thus, many leading experts in this field are associated with biomedical and pharmaceutical companies; they obtain funding for their projects or independently founded the companies dealing with this technology or are included into scientific and consultation councils being interested in approval and advance of this technology into the market, including the global market of biotechnologies.

Thus, a conflict of interests arises as part of social propaganda and development of state policy in the area of human heritable genome editing. In this case, a conflict of interests is a set of conditions, in which professional judgement about primary interests (a patient's well-being or study validity) tends to depend on secondary interests (such as financial benefit) [18]. As a rule, conflict of interests in biomedical studies and medical practice occurs because of financial relationships between scientists, medical workers and representatives of commercial organizations such as pharmaceutical companies. Effect of commercial interests on biomedical studies in the area of human genome editing is widely discussed nowadays [19, 20].

It is important to differentiate between conflicts of interest and conflicts of liabilities. The latter arises because of professional commitments, but not because of conflicts between primary interests (professional obligations) and secondary interests (financial stimuli and recognition). For instance, conflict of liabilities can include a professional liability to give equally distributed time and attention set by the contract to researches, teaching, administrative liabilities, scientific communication and social propaganda. It is easy to image a conflict of liabilities of a scientist who tends to comprehend a certain aspect of human embryo development and is included into the Ethics Committee which has to develop the guiding principles for human embryo studies. It can appear that research interests can produce a negative effect on the moral estimation of human embryo experiment acceptance.

Expert and scientific councils have particular influence during the debate about the use of genetic editing in clinical practice. Experts participate in scientific communication supplying non-professionals with empirical data and knowledge about technologies of genetic editing to solve the ethical problems. But the problem is that experts can be influenced by conflicts of interests and conflicts of liabilities, just like it was with the Chinese scientist.

In particular, if scientists (experts) organized biomedical companies, they display strong interest in acceptance of scientific achievements of their colleagues. So, the approval to use the genetic technologies can be associated with their personal financial and other incentive. It is important to consider that the concept of legal regulation is formed during discussions at any possible scientific conferences and summits (for instance, the third International Summit on Editing the Human Genome will take place in March 2023). Decisions are taken by a group of scientists and experts, many of whom can have a conflict of interests and liabilities, which is a serious threat to epistemic and ethical integrity of taking decisions in this regard.

While regulating the CRISPR/Cas technology, little attention is currently given to commercial conflicts of interests and

conflicts of obligations among biomedical researchers. The Chinese scientist is not the only example, other scientists can probably try their possibilities in human genome editing. Thus, Russian scientists Denis Rebrikov also reported gene editing with the goal of altering deaf gene [12].

It is important to accept that concentration on perspectives of human genome editing in clinical practice during the next 10 years ignores the fact that developments in other areas of biomedical studies require much more time to be approved for clinical use. For instance, FDA have approved only one clinical therapy based on human stem cells by now, i. e. transplantation of hematopoietic stem cells [21].

Thus, it is essential to regulate the issues while conducting the studies, take stricter protective measures regarding disclosure of data about the conflict of interests and conflict of liabilities of the leading experts in the area of human genome editing. It should be taken into consideration that current data about commercial conflicts of the leading experts is inaccessible or minimal, that conflicts of interests are not disclosed during studies, which makes it difficult to comprehend real economic interests while maintaining certain research positions among participants of public discussions. Thus, while drafting the legislation it is impossible to rely upon objective data and results free from the effect of secondary factors to develop standards that regulate the use of genetic modifications with human genome.

The measures that can promote the integrity and political legitimacy of taking decisions in legal regulation of human genome genetic editing technologies should be taken into account.

The scientists need to disclose data about conflicts of interests and conflicts of liabilities in public and in a more detailed mode. For example, the project named Dollars for Professors [22] started in Sept. 01, 2021. It reflects commercial conflicts of interests, but the base of today is not complete enough though the project itself can be considered as positive practice.

The practice needs to be expanded. A common register of conflicts of interests for researchers can be created on the WHO basis. Moreover, we can establish the rule in accordance with which study financing agencies and companies will have to submit data about a conflict of interests and liabilities.

The case with He Jiankui shows that science can't effectively foresee the danger of using the technologies of human genome editing and need in organized work regarding the formation of the national and international legislation. That's why the desire of many countries to acquire the leading positions in the area of biomedical and genetic technologies and build an international dialogue is important in spite of many controversies between scientific societies and countries, as human genome editing involves everyone and the future generations, variety of the human society and safety of life and health.

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# ETHICAL ASSESSMENT OF GENOME EDITING APPLICATIONS IN ONCOLOGICAL PATIENTS

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Further development of genetic engineering improved the chances to defeat deadly disorders due to discovery of innovative methods of treatment of various diseases, including oncological ones. In doing so, the methods have to go through clinical trials; they are not safe today. In fact, a paradox emerges: the trials are necessary, but they can't be approved in accordance with regulatory requirements, as the risk for the subjects is higher than the benefit. For oncological patients, clinical trials, however, are the last chance for salvation. This requires an additional ethical discussion regarding approval of ethical expertise by the corresponding authorities in these exceptional cases. In this regard, the author of the article provides an ethical assessment of human genome editing applications from the point of view of risk and benefit for a subject and community of subjects, taking into account such ethical principles as 'human priority', 'precautionary principle' and 'principle of responsibility to future generations'.

**Keywords:** morality, bioethics, ethical principles, genome editing, treatment of cancer patients, the precautionary principle, the principle of responsibility to future generations

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# МОРАЛЬНАЯ ОЦЕНКА ПОСЛЕДСТВИЙ ИСПОЛЬЗОВАНИЯ ТЕХНОЛОГИЙ РЕДАКТИРОВАНИЯ ГЕНОМА ОНКОЛОГИЧЕСКИХ БОЛЬНЫХ

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С развитием генной инженерии появился шанс одержать победу над смертельными болезнями благодаря открытию инновационных методов лечения различных заболеваний, в том числе и онкологических. При этом методы должны пройти клинические испытания, и на сегодняшний день они небезопасны. Возникает парадокс: исследования необходимы, но согласно регулятивным требованиям и предписаниям разрешить их нельзя, так как риск для испытуемых в данный момент выше, чем польза. Однако клинические испытания, например, для онкологических больных являются последним шансом на спасение, и это требует дополнительного этического обсуждения в плане разрешения проведения в этих исключительных случаях этических экспертиз соответствующими инстанциями. В этой связи автор статьи дает нравственную оценку последствий использования технологии редактирования генома человека с позиции пользы/риска для отдельной личности и сообщества индивидов, опираясь при этом на такие этические принципы, как «приоритет человека», «принцип предосторожности», «принцип ответственности перед будущими поколениями».

**Ключевые слова**: мораль, биоэтика, этические принципы, редактирование генома, лечение онкологических заболеваний, принцип предосторожности, принцип ответственности перед будущими поколениями

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Searching effective methods of treatment of oncological diseases is a strategic task of modern medicine. Traditional methods of struggling with the developing tumor that have been used by physicians for a long time include surgical treatment (complete tumor removal), radiation therapy (tumor radiation), and chemotherapy (use of medicines that inhibit rapid cell division). The methods do not always provide for the desired outcome, as a surgery does not warrant complete tumor removal, whereas radiation therapy and chemotherapy can kill healthy cells and result in decreased immunity and other serious outcomes, including a patient's death. That is why doctors and scientists across the world started seeking alternative methods of treatment. Deepened knowledge of tumor genetic features and rapid development of genetic engineering opened up new horizons to treatment of oncological diseases.

Thus, virotherapy (viral oncolytic therapy) is not an innovative alternative method as it was developed in the second half of the XX century. At that time, however, medicine had to deal with naturally occurring viruses only, that's why the antitumor effect was short and unstable. Moreover, 'the lack of a normal virus-specific immune effect consistently worsened a patient's condition' [1]. It significantly, up to oblivion, inhibited development of virotherapy and only gene engineering opened up new prospects for it, because the majority of developed methods and technologies

focused right on cancer treatment. Today, genome editing is the most perspective method in this regard [2], even though the possibilities of its application are limited, and these ethical and medical discussions raise more questions than they answer.

Technological approaches to human genome editing appeared at the end of the last century. However, the principal achievement included development of CRISPR/Cas system by J. Doudna and E. Charpentier who obtained the 2020 Nobel Prize for that. They examined Cas9 exposure on bacteria and showed that 'any DNA molecule, including human DNA, can be cut at any point' using a certain mechanism. That was a revolutionary discovery. CRISPR/Cas system made it possible 'to introduce point mutations, integrate new genes at certain sites or remove parts of nucleotide sequences, correct or substitute gene fragments' [3].

Thus, CRISPR/Cas9 gave hope for salvation to millions of people. We have already succeeded in treatment of certain types of cancer by now. Physicians managed to obtain immune cells of a patient and alter their genetic defects that would not allow them to struggle with tumor antigens [4]. According to Stadtmauer E, this may be evidence of safe genome editing [4], as only necessary cells, but not the entire human genome, are edited in this case. Thus, apparent safety is not real safety, that is why there is no reason to discuss early integration of CRISP-technology due to opposite opinions of scientists [5]. Thus, He Jiankui, a Chinese scientist, used the CRISPR/Cas9 system to conduct clinical trials with human embryos. The fact was made available to the public and had serious disputing resonance. In spite of certain success, gene editing could result in DNA errors: according to genetic scientists, there is a risk that the errors will be inherited. In this regard, such world-famous journals as Nature and Science refused to publish the results obtained by Chinese scientists referring to non-compliance with ethical and legal standards of the trial and lack of uniformity regarding the borders of using the genome editing technology [6].

Nevertheless, clinical trials are required to introduce any technology; it is impossible to assess its safety without them. So, the 'ethical risk' is inevitable in case with CRISPR/Cas9 as well, which calls for ethical assessment on the part of benefit/risk for the subjects.

Every person tries to live longer. When coming across such a restriction as a deadly disease, the person thinks of experimental methods of treatment and possibility to participate in clinical trials with some advantages and shortcomings. The principal advantage for the participants includes access to novel medications and technologies, which are currently inaccessible to other oncological patients. There is a chance that they will be effective and that the patient can prolong his life. Moreover, the level of control over such a patient is much higher than that during standard therapy. This would certainly have an effect on taking a decision. The altruistic factor is important here as well. It is associated with contribution to the trial by the patient which makes our knowledge of oncological diseases deeper and more expanded, saving lives of others in the future.

The benefit of CRISPR/Cas9 system is doubtful for sceptics only, as previously incurable diseases will turn into curable ones owing to correction of genes. This can have negative, and probably irreversible impacts, as correction of certain gene mutations can affect occurrence of others (just like with the Chinese scientist's experiment); the genetic perspective is not always known. The technology of genome editing can be successful for some patients and useless for others. Nevertheless, the trials are necessary and many oncological patients agree to use the chance. But is it ethical in relation to them? Can we mention a voluntary, rational and weighed solution in this very case?

In this regard, ethical assessment of using the method of human genome editing should be performed from the perspective of a certain personality who has a right to live and from that of the society of people considering potential risks and benefits, as any human genome transformation can result in both positive and negative consequences with different modalities. In this case, according to Jonas G, the rule 'of advantage of unfavorable prognosis over favorable one' should be applied on a constant basis. Thus, we need to be 'more attentive to the prophecies of disasters than to the prophecies of welfare' [7]. It is obvious that modified genes are inherited, and the human genetic pool can be altered. Two ethical issues that arise are as follows: the issue of the right to experiment with human beings of the future and the issue of how and to which extent genetic control over a human of the future can be implemented. They are now subject to the ethical 'do no harm' restriction and regulated by the 'precautionary principle', which is synonym to the rule by Jonas G. According to Yudin BG, the principle should be applied when safety of a new biomedical technology is doubtful. The last one can be used only when scientists can provide solid arguments in favor of benefit over possible risks [8]. In case with genome editing technology, no such risks are available yet. Moreover, the consequences can be unpredictable for the future genetic pool and concern 'the roots of the entire human enterprise' [7]. Thus, global mistakes and failures must be excluded. Following pragmatic purposes, however, a human being re-estimates his own mind, and his attempts to submit and control over own evolution are overconfident. That is why the moral attitude 'to preserve the legacy of prior evolution' is still pressing because the heritance is not that bad for the people of today.

Ignoring the technology safety for the benefit of an individual, we form the lottery effect based on the 'non-reliable' 'or-or' principle, though as per art. 3 'Human priority' of Strasburg Additional protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research as of 2005, 'the interests and welfare of a subject participating in the trial prevail over the interests of science or society' [9]. The same provision is set in the Model Law 'On protection of human rights and dignity in biomedical trials in member states of the CIS': 'it is acceptable to conduct human biomedical trials if direct benefit is obtained' [10]. Thus, it is not allowed to conduct the trials that provide primary benefit to other people or contribute mainly to progress in science.

Let us consider the situation on the part of benefit for an individual: it is not obvious, but it can occur so. Thus, the principle of 'human priority', principle of humanism that gives the human the status of absolute value, comes into collision with the principle of 'responsibility to future generations', which raises the following question: 'Can I participate in a lottery that affects interests of other people?'. The point is that close genetic intermingling in a human community enables to draw a conclusion that it is practically 'impossible to avoid not influencing the destiny of other people by my actions' [7]. Going big in case of a clinical trial which is the last hope for an oncological patient, the subject indirectly counts upon something that belongs to somebody else. It means that personal interests prevail over public interests, which is primarily based on his comprehension of ethics and feeling/not feeling such an emotion as guilt. Can we consider the decision ethically justified?

Arguing about potential risks for the entire community of individuals, we mentioned the 'no-harm' principle, which is universal and global, and in the case with genome editing its particularization is not possible yet. In the opinion of Apresyan RG, this principle 'is of an objective and impersonal nature', similar to any other ethical requirement [11]. Though it is valid for everyone, it can't grasp the entire richness of real-life

situations, ignoring the right of an individual to a life and his possibly only chance to prolong this life even at the expense of such risk. Moreover, the same Additional protocol states as follows: 'a human trial can be conducted only when there is no effective alternative to this method' [9], which is true at the terminal phase of an oncological disease. So, the principle of 'responsibility to future generations' is a doubtful critical point for a common man who takes the decision.

The principle often results in regulative moral prohibitions adding to the 'precautionary' principle. At the same time, the principle initiates many actions extending beyond the 'here and now' ethics but having an ethical justification while mentioning welfare of a human being in the future. However, everyone of us has moral obligations and responsibility to people we contact and interact with; we expect the same from those around us because of our idea of a moral obligation. This is how the golden rule of ethics is applied in its primitive sense. It is not applicable to the future generations due to the lack of reciprocity. In case of an immoral deed, a person waits for conviction or at least pretension on the part of the recipient of these actions. The 'non-existing' future can't lay any claims, because it has no rights at this very moment. In this regard, the following questions arise: 'What has the future done for me? Does it observe my rights?' [7].

It is obvious that ethics is about reciprocity. It is manifested through the social 'human-human' relations, that's why the 'human being-future human being' linking goes beyond the range. There are cases when ethical activities are a priori unresponsive, for instance, ethics of care towards own children. Such ethical features as unselfishness and altruism are always manifested in this case and the principle of responsibility to future generations acquires the status of 'obligation to the offspring'.

Nevertheless, the question remains open: human genome editing can't be introduced without clinical trials. It is not safe today. The way out is a trial with voluntary participation by people with untreatable diagnosis. The thesis is immoral as it is, because in accordance with the Additional protocol, human benefit from conducted trials and experiments should significantly outweigh the risks and negative effects. Does it mean that the destiny of a patient with terminal illness is predetermined? How can the patient accept and morally agree with the prohibition of clinical trials based on responsibility to the future on a rational basis, if his life is determined here and now, this being the only chance? On the other hand, taking into account the lack of the 'right to suicide' in a human being, the lottery is far from being immoral, as a number of oncological patients and patients with inherited diseases is exponentially increasing. That is why in case with the person of the future, the immoralism can be substantiated from an ethical point of view. In fact, the 'moral luck' is always associated with an 'ethical risk': absolute moral prohibitions of deontology do not operate on the constant basis when it is about the life of an individual. So, in this case those who take a decision about the use of genome editing should refer to the utilitarian and pragmatic practice.

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## GENETIC TESTING IN HEALTH CARE PRACTICES (ADAPTED FROM AN EMPIRICAL STUDY)

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The article contains the results obtained during an empirical study of health care practices among people of a large Russian city implemented in a combined strategy in 2020–2021. Our focus remains on the reference of citizens to the procedure of DNA diagnostics as a novel instrument of health-saving behavior and attitude to genetic knowledge in general. The obtained data allow concluding that genetic testing is not widely popular among population today, as only 9,5% of those interviewed have ever done it. DNA diagnostics is more frequently used by young women and men with high income and don't trusting modern medicine, which probably reflects the actual condition of the market of genetic services in our country. Apart from financial possibilities, involvement into consumer genomics is influenced by insufficient trust in DNA information, and suspecting that players on the market of genetic services obtain economic profit. However, the most important argument against it consists in the discovered discrepancy between perception of genetic data as something inevitable and currently popular ideology of healthy lifestyle, meaning that a person can influence the outcome of the efforts made. As a result, research participants are not willing to become the everlasting 'patients-in-waiting' even in case of existing symptoms, but implement their 'right not to know'. Under these conditions, an important task includes organization of active promoting awareness that unlocks potential, capabilities and limitations of genetic diagnostics.

**Keywords:** genetic testing, health care, telephone survey, semi-structured interviews, patient-in-waiting, social attitudes

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## ГЕНЕТИЧЕСКОЕ ТЕСТИРОВАНИЕ В ПРАКТИКАХ ЗАБОТЫ О ЗДОРОВЬЕ (ПО МАТЕРИАЛАМ ЭМПИРИЧЕСКОГО ИССЛЕДОВАНИЯ)

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Статья содержит результаты эмпирического исследования практик заботы о здоровье жителей крупного российского города, реализованного в комбинированной стратегии в 2020–2021 гг. В фокусе нашего внимания обращение горожан к процедуре ДНК-диагностики как современному инструменту здоровьесберегающего поведения, а также установки в отношении генетического знания в целом. Полученные данные позволяют заключить, что сегодня генетическое тестирование не пользуется широкой популярностью среди населения, лишь порядка 9% опрошенных когда-либо прибегали к нему. К ДНК-диагностике чуть чаще обращаются молодые женщины, а также мужчины, имеющие более высокий доход и не доверяющие современной медицине, что, вероятно, отражает состояние рынка генетических услуг в нашей стране. Помимо финансовых возможностей на вовлечение в потребительскую геномику влияют недостаточное доверие информации о ДНК, а также подозрение игроков рынка генетических услуг в получении экономической выгоды. Однако наиболее важным аргументом «против» выступает обнаруженное расхождение между восприятием генетических данных как приговора и культивируемой сегодня идеологией здорового образа жизни, предполагающей способность человека влиять на исход собственных усилий. В результате участники исследования не желают становиться пожизненными «пациентами-в-ожидании» даже при имеющихся симптомах, а реализуют «право не знать». В этих условиях важной задачей становится организация активной просветительской работы, раскрывающей потенциал, возможности и ограничения генетической диагностики.

**Ключевые слова:** генетическое тестирование, забота о здоровье, телефонный опрос, полуструктурированные интервью, «пациент-в-ожидании», социальные установки

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**Соблюдение этических стандартов:** в ходе исследования соблюдались общие этические принципы: обеспечение конфиденциальности и анонимности участников, получение информированного согласия.

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Novel therapeutic and preventive technologies made possible owing to success of genetics achieved in recent decades are becoming widely spread today. First and foremost, it's about DNA diagnostics that reveals the risk of various, primarily hereditary diseases. In the light of pressing discoveries, genes become the main embodiment of risk, but not the body itself [1]. Thus, using the potential of genetics is considered as a significant aspect of well-being control. As a result, on the one hand, a person obtains instruments for better, modern and technologically advanced health care. On the other hand, use of innovations entails burden of additional responsibility and need to participate in medical decision making.

Applying DNA technologies in medical practice gives birth to a set of complex ethical, philosophical and legal

issues comprehended by representatives of socio-humanistic disciplines [2, 3]. It is much more rarely that investigators examine how genetic knowledge penetrates the daily life of a modern person, and how it is used or rejected. Though important empirical studies of professional culture of genetic scientists and their communication with patients appear to date [4–7], a general picture of using genetic innovations in our country remains unclear. The work by Yu. Voynilov and V. Polyakova [8], which shows that the Russians are rather suspicious about biomedical technologies, is an exception that proves the rule.

As the areas of using genetic research go far beyond orphan diseases, their prophylactic and preventive potential for the entire population is stressed (especially in case of consumer genomics). It is important to understand the extent to which the Russians use the novel scientific achievements to care about their health, how they follow the obtained recommendations and what attitudes they have towards genetic knowledge in general. In this article, we'll try to answer the questions, relying on the results of the empirical study with inhabitants of a Russian megalopolis.

## EMPIRICAL STUDY DESIGN

To find out and describe how (biomedical and digital) innovations are used by modern citizens in the practices of health care, a combined empirical study was implemented. During the first stage, 90 semi-structured interviews with citizens of large Russian cities (mostly Saint-Petersburg, Moscow, Ulyanovsk, Petrozavodsk) applying different technologies of health care were conducted in August 2020 — April 2021. Informants manifesting significant activity and being aware of health issues are in the center of attention. A question about the experience of DNA diagnostics was asked in 17 interviews. Study participants were selected based on the method of available cases with subsequent use of the snowball effect. A part of the interview was held in the distance mode using such platforms as Zoom, Skype, MSTeams, WhatsApp.

The questionnaire for phone survey of Saint-Petersburg's residents implemented at the second stage of this research in August 2021 was developed based on the results obtained during the interview and with the aid of the Resource Center of the Scientific Park of Saint-Petersburg State University 'Center for Sociological and Internet Research'[1]. Representativity was determined in a quota sample by gender and age. The data were processed using SPSS Statistics (ver. 23) with implementation of method of correlation analysis (Spearman's test). $P$ (Sig) < 0.05 was considered significant. Correlation coefficients were estimated with the Chaddock's scale. Though the found interrelations were weak, they resulted in reasonable suggestions about the processes currently occurring in the sphere of health care.

Qualitative and quantitative methods combined in this research provided a complex idea of new practices of health-saving behavior. On the one hand, common tendencies were described and general population was characterized. On the other hand, semi-structured interview results enabled a deeper interpretation of digital data providing contexts not discernable behind the common distributions.

17 interviews with informants aged 26 to 69 (2 men and 15 women) were utilized at the first stage. Phone interview respondents were represented by 861 people with 56.2% of women and 43.8% of men. Among them, 21.7% were 18–29 y. o., 19.9% were 30–39 y. o., 15.8% were 40–49 y. o., 17.7% were 50–59 y. o., 25.0% were 60 years of age and older. About a half of those interviewed (51.7%) complained of chronic diseases. As basis for this research were citizens of Saint-Petersburg with a higher level of life as compared with many Russian cities, the results can't be applied to the entire population of the country. At the same time, they can characterize citizens of other large Russian cities with a certain degree of conditionality.

Though we mainly concentrated on digital technologies, study participants were asked questions about experience in genetic testing as well. We tried to describe the variety of using innovative technologies by citizens to take care of their health. In this article, only one situation was considered: experience in DNA diagnostics irrespective of motivation, both in the presence of symptoms, and for prevention and prophylaxis.

## STUDY RESULTS

9.5% of those interviewed (9.1% of men and 9.9% of women) underwent genetic testing to find the risks of development of different diseases. The majority of them did it more than one year ago. COVID-19 pandemics could influence the parameter by shifting priorities in health care towards the new virus. Nevertheless, it is obvious that the rate of using genetic technologies to care about the health of megapolise inhabitants is not large yet and significantly yields to the use of digital technologies by popularity. As a comparison, 48.7% of respondents have ever done digital self-tracking, 32.5% visited forums and social networks devoted to health issues, 25.2% used telemedicine.

There were no fundamental differences in referral to DNA diagnostics depending on education, marital status, estimation of well-being by a respondent, control locus regarding health and presence of chronic diseases. Meanwhile, certain variations were found in the groups of men and women as far as the use of technology goes. In women, the practice of genetic testing is associated with age: the rate of referrals is slightly decreased with aging (0,115[2]), which is explained by involvement of women into the field of reproductive genetics [6]. During the interview, the informants noted that they came across genetic testing while being pregnant or in case of reproductive disorders: '*except for screening during pregnancy, that's all'* (W, 39).

In certain cases, a husband entered the area of 'genetic control' as well: '*Listen, it wasn't me, but my husband who did the testing. After an unsuccessful pregnancy he did some genetic testing to find out whether he had genetic abnormalities. When he was told that it was OK, he calmed down and went on living. And a healthy child was born'* (W, 34).

The study participants failed always to explain the meaning and results of these examinations. Women who didn't have an experience in DNA diagnostics are often informed of the procedure possibilities, plan to use it while getting ready for the birth of a baby and consider the step important: '*Yes, I heard about it, this is rather interesting. I didn't do the testing. But I will do it when I decide to have a baby. I mean, to know about genetic diseases'* (W, 32). We believe that the current market of reproductive genetics remains one of the most popular and demanded.

Among men, weak, but statistically significant correlations are reported between involvement into DNA diagnostics and

[1] Here and elsewhere, it's Spearman's test p<0.01, unless otherwise stated

[2] Frequency of using certain practices is measured according to the scale from more specific to less specific resulting in a negative correlation coefficient in case of positive connection direction.

income level: the procedure is more frequently used by those with a better financial and economic situation. One of indirect parameters of material wealth is a possibility to obtain medical assistance based on VHI program or on a fee basis. In spite of the fact that for the whole sample obligatory medical insurance is particularly popular, among the men who have ever done genetic testing, 42.9% made a last visit to the doctor on a paid basis (while obligatory medical insurance was used by 34.3% only) vs 22.5% of those who have never done this testing (0.186[3]). Thus, genetic testing among the group was more strongly sought for by those with a higher income and who can refer to commercial medicine. High cost of genetic testing as a sound reason for its refusal was mentioned by informants during the interview, as shown below. The lack of trust in healthcare and need to (re)check the diagnosis and medical recommendations belong to a factor of finding genetic health risks among men. In this group, the procedure is more frequently used by those who rechecked medical prescription during the last year (0.147). DNA diagnostics is probably considered as an instrument that satisfies the need of modern patients in their well-being control and incentive to find out the reasons for its worsening.

One of the key objectives of this study is to detect combinations between various health promoting practices. As a result, it has been found out that the use of genetics potential is associated with involvement into certain digital and traditional ways to support good health. And again, slight differences in the groups of men and women are observed. Experience of genetic testing is related to searching information on the Internet (0.114) in men and to visiting forums and online communities devoted to health issues in women (0.119). Moreover, men who underwent DNA diagnostics (0.179) are more prone to share information about convalescence or living with illness in social network than women (0.109). Both men and women combine genetic testing with telemedicine (0.142 for men and 0.134 for women). Meanwhile, men tend to correlate DNA diagnostics with such modern methods of health care as control of nutrition (0.116) and attention to mental well-being (0.170). It can be seen that determining health genetic risks is currently included into a wider repertoire of good health support practices and combined with digital and traditional options. Those interviewed who mentioned the experience of genetic testing manifest significant activity in relation to other modern practices of health saving behavior. Besides, the found relations between the biomedical and digital technologies can be explained by the use of the latter to obtain data about the possibilities of genetics. The fact was also mentioned by informants during the interview.

If analysis of quantitative data allowed to reveal and describe some general regularities of genetic testing prevalence among citizens of a large city, then the interview results enable to frame assumptions about social attitudes regarding this technology and motives of its using (not using). Informants included people who participated in the procedure of DNA diagnostics as well as those who had no similar experience; who were aware or poorly aware of these possibilities. We were interested in situations and complex trials such as compiling DNA profile and determining the risk of a certain disease development. During the interview, the issue of using the potential of genetics to obtain data about the origin and mapping resettlement of ancestors was discussed. However, we won't go into detail about this. It should be noted that in this case the procedure is assessed as entertainment, and the obtained data are considered as unreliable and inaccurate.

When analyzing qualitative data, types of attitudes to genetic diagnostics were identified. They were determined considering the presence or absence of experience in a similar procedure. Among informants who have never had DNA testing, there are proponents and opponents of genetic screening: those who plan to use it in the future and those who believe that the procedure is useless. Counterarguments can be systematized as follows.

1) High cost of a complex genetic testing. Access to technologies depends on financial capabilities and region of the person. Though citizens of large cities have certain advantages in this respect, the cost of services is considered significant for them as well. '*On the one hand, I didn't do the testing because it is very expensive, but it is not that simple. A complete screening costs a pretty penny'* (W, 39). Economic resources influence the decision to select a set of separate parameters for diagnostics: '*Not a complete testing, as it is expensive. I am not ready to pay a fantastic sum for it*' (W, 42).
2) Distrust in the obtained results, which are considered as unreliable. The unreliability can be interpreted in two ways. First, genetic knowledge is perceived as doubtful and insufficiently authoritative. We suggest that certain contribution into such comprehension of genetic data ensures its penetration into media space (social networks, television). '*You know, genetic testing goes like this: my grandmother and mother both had vegetative vascular dystonia, I was diagnosed it too, but finally a genetic disorder was found' (laughing)* (W, 29). Second, the companies that provide the services of DNA diagnostics are suspected of pursuing mainly economic interests and getting profit. '*No, I believe that all these centers have only one purpose of making as much money as possible. They tell a pack of lies'* (M, 53). Those who promote genetic testing are suspected to have a hidden agenda as well. '*No, no, I heard, but I didn't pass, and there was no thought of passing such a thing. It seems to me that this is more of an advertised event, and even considering that it is being done, at least I have come across, well, no one from my friends has done it, and what I see is, let's say bloggers do it for advertising, this is more of an advertising move, a trick'*. (W, 39).
3) Unwillingness to know the results of DNA diagnostics, certain health fatalism. The informants are not aware of their risks and prefer to remain in the dark following the principle of '*what you don't know can't hurt you'* (W, 35). Though they understand the advantages of genetic testing such as prevention and prophylaxis, study participants explicitly refuse from the possibilities as they don't want to live waiting for the disease. '*… I am afraid of these results, because it seems to me that when you know about the Parkinson disease, that will affect you in the future, you can learn to appreciate what you have today. It's better to have what to remember, than to wait for something bad to happen… Now, in one year or 10 years. It's like playing ostrich, though. Because some diseases can be prevented if you know the predisposition'* (W, 39). The key meaning of this argument is to avoid information about the disease until the symptoms and accordingly anxiety are manifested ('*I don't want to know about that*' (W, 31; W, 39)) and unwillingness to become 'a patient-in-waiting'. '*How can I continue living if I know about something bad?*' (M, 39). It is important to note that in this case the informant commonly determines on his own whether he needs the procedure

[3] Frequency of using certain practices is measured according to the scale from more specific to less specific resulting in a negative correlation coefficient in case of positive connection direction.

and doesn't communicate with a doctor. '*No, doctors never say things like that. I found it out on the Internet. It wasn't a doctor who told me this'*. (M, 39). Though the study participants show significant activity and awareness about health preserving issues and use different modern technologies for that, it is the consequences of genetic testing capable to cause changes in their lifestyle and self-perception that are of the utmost concern.

Although the 'fatalistic' ideas are popular, some of those interviewed reported their intentions to refer to DNA diagnostics in the future following the principle 'forewarned is forearmed'. '*Unfortunately, I haven't taken the test, but I would like to take it. I'm interested in this story. I heard many opinions, and not everyone trusts it. It just kept out of my way, or I saw it when I couldn't afford it. But I believe the testing is important, considering the possible hereditary risks'* (W, 28).

The sampling also included informants experienced in genetic examinations. However, they have different attitudes towards the use of obtained data.

1) Information acquired during complex diagnostics is an element of identity and gives a sense of control over health and life in general. '*I don't like surprises. I want to know it all beforehand. Then I can be ready for anything. Knowledge is a determinant factor to me. If I know, I will act somehow. Or I may not act, but with my informed consent'* (W, 26). Health turns into achievement being a result of hard and day-to-day work. In this case, a family nature of genetic testing is manifested through informants' narratives [9]. '*I am interested in cool things, like whether I have a genetic predisposition to muscular dystrophy or loss of vision or hearing, I don't remember which one. It is really important, because later we can both have the test and understand what genetic information can be passed to our children'* (W, 26). It should be noted that it is the patient who acts as an initiator of complex genetic screening.
2) The situation looks different in case of genetic determination of the present diseases. As a rule, in this case the procedure is carried out following a doctor's recommendation, and the obtained data are not used and do not change the informant's lifestyle. Genetic data are considered as something inevitable, guidance for inactivity; there is a conviction that nothing can be changed. '*It wasn't my initiative… I obtained a positive result… When I first knew about that, I was very upset, because of very unpleasant perspectives. I was nervous. If the disease could be arrested, I would arrest it. But it's genetic, and no arrest is possible. I know that all methods of struggling with it will be used in vain. My neurologist told me that it was impossible. I am not waiting, but I understand that it is similar to death. You understand that you'll die. You don't know when. Are you waiting for the death to come? No. But you understand that it's inevitable*'. (W, 42). It can happen that the existing symptoms don't impair the informant's life quality, and DNA data do not change his/her lifestyle. '*I have a genetic disease. To confirm it, I needed to do genetic testing. I did it and the disease was confirmed. It was about a certain disease that was suspected. But I use the information because doctors need it to understand that I don't have hepatitis. I inform them of it on a constant basis so that they don't worry if my skin turns yellow and this produces no influence on my lifestyle'* (W, 37). The fact that the idea of DNA diagnostics belongs to a doctor, but not a patient, influences motivation of the latter and implies subsequent using (non-using) of the data, which is alienated from the informant.

## CONCLUSIONS

Based on the results obtained during the empirical study it can be concluded that genetic testing is currently not widely popular among population, as only 9,5% of those interviewed have even done the testing. Although traditional social and demographic parameters and certain values of health behavior do not determine involvement in genetic testing, differences in the groups of men and women were revealed. DNA diagnostics is slightly more popular among young women and men with a higher income, and do not trusting modern medicine. We suggest that the discovered variations reflect the condition of the market of genetic services in our country. The segment of reproductive genetics is the most developed one. Access to consumer genomics is determined by financial and economic possibilities. The use of genetics potential is embedded into a wide repertoire of modern ways of health promotion with digital practices being the most popular among them.

Apart from financial possibilities, involvement into consumer genomics is influenced by not sufficient trust in genetic information and suspicion that players of the market of genetic services pursue economic purposes. But the most important disadvantage is that genetic information is perceived as sentence, which is not known by the study participants until it is put into execution (when the symptoms occur). The attitude is rather interesting because it can be traced in those who acquired values of a healthy lifestyle and demonstrated intense self-care. Informants avoid genetic information because risks and health mean the same as the presence of a disease and genetic profile respectively. It makes any activity associated with their own well-being meaningless and creates a sense of losing control over their life. One of the most important principles of healthy lifestyle ideology is an ability to improve health and prevent diseases using various practices and manipulations; the future is not predetermined; it is open for different variants that depend on the efforts taken by a person. In case of genetic testing, there is a firm belief that the future can't be changed. This must be the reason for higher popularity of digital technologies that make people confident about possible control of their health and well-being. As a result, study participants don't want to become the everlasting 'patients-in-waiting' even in case of existing symptoms, but implement their 'right not to know'.

We assume that the discovered attitudes to DNA diagnostics can be explained by insufficient notification of general public of a probabilistic nature of genetic knowledge and multifactorial type of the most diseases. As a rule, a patient comes to know about the potential of genetics from the Internet and mass media, and takes a decision about the testing independently. When a doctor (who is commonly not a genetic professional) recommends the procedure, he shares an opinion about the inevitable nature of the obtained results and the future of the patient.

Paradoxically, that widely spread ideas about genetics contradict the cultivated healthy lifestyle ideology when a person can improve his/her health. Thus, impediment for turning the practices of genetic testing into routine consists not in sufficient readiness of a patient for active self-care, but in a need for producing a possible influence on the outcome of own efforts. Without promoting awareness that exposes potential, possibilities and limitations of genetic testing, close 'doctor-patient' communication, attaining genetic knowledge by non-major medical professionals, involvement of population in DNA diagnostics will remain a complex task.

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## SOCIO-PHILOSOPHICAL DIMENSION OF EPIGENETIC RESEARCH

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In the last 20 years, epigenetics has evolved into a relevant and rapidly growing area of science. Scientific achievements in this area stirred interest among representatives of numerous socio-humanitarian disciplines, creating discussions at the legal, philosophical, political, social, cultural, medical, commercial and other levels. Thus, epigenetics is an outstanding example of a modern trend towards interdisciplinary trials as it is becoming a 'borderline object' of different sciences. In this article, the author analyzes the unfolding discussions regarding assessment of ethical, social and legal effects of epigenetics. Representation of epigenetics in mass media and science has been considered. Particular attention has been given to the reasons for epigenetic antideterminism. The epistemic value of epigenetics offers a different perception of some fundamental concerns such as the nature-upbringingnurture dichotomy, appropriate social politics, in particular, in the area of health, ethical contradictions when assessing harm and benefit, collective and individual responsibility (especially parental one), and the issue of non-identity. The author notes that in spite of the potential of epigenetics in personalized medicine, the exceptional phenomenon of epigenetics should be treated with caution due to early stages of the research and insufficiency of empirical data. Unreasonable extrapolation of epigenetic regulation to the sociocultural life can result in false reductionist conclusions. Nevertheless, the author is quite optimistic about the perspectives of epigenetic studies.

**Key words**: bioethics, epigenetics, ELSI, theory of justice, political theory, determinism, responsibility

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## СОЦИОФИЛОСОФСКОЕ ИЗМЕРЕНИЕ ЭПИГЕНЕТИЧЕСКИХ ИССЛЕДОВАНИЙ

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Эпигенетика в последние 20 лет превратилась в актуальную, активно развивающуюся отрасль научного знания. Научные достижения в данной области вызвали интерес представителей множества социогуманитарных дисциплин, сформировав дискуссии на нескольких соответствующих уровнях: правовом, философском, политическом, социальном, культурном, медицинском, коммерческом и пр. Таким образом, эпигенетика становится одним из ярких примеров современной тенденции к междисциплинарным исследованиям, став «пограничным объектом» разных наук. В данной статье автор анализирует разворачивающиеся дискуссии в оценке этических, социальных и правовых последствий эпигенетики. Рассматривается репрезентация эпигенетики в СМИ и науке, отдельное внимание уделено причинам формирования представления эпигенетики как «антидетерминистской». Эпистемическое значение эпигенетики позволяет по-новому обратиться к ряду фундаментальных проблем: дихотомии природа-воспитание, вопросам о справедливой социальной политике, в частности, в области здравоохранения, этическим противоречиям в оценке вреда и пользы, коллективной и индивидуальной ответственности (особенно родительской), «проблеме неидентичности». Автор отмечает, что несмотря на потенциал эпигенетики в персонализированной медицине, к феномену эпигенетики, как исключительному, следует относиться с осторожностью ввиду ранних этапов исследования и недостаточности эмпирических данных. Неоправданная же экстраполяция эпигенетического регулирования на социокультурную жизнь может приводить к ошибочным редукционистским выводам. Тем не менее он оптимистично смотрит на перспективы эпигенетических исследований.

**Ключевые слова:** биоэтика, эпигенетика, ELSI, теория справедливости, политическая теория, детерминизм, ответственность

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Academician Frolov IT wrote as follows: 'Biological cognition, just like any other cognition, is a deeply social subject and object interaction process, during which complex social and ethical research principles have been elaborated for centuries' [1].

The Human Genome Project launched in 1990 let us hope for a new paradigm of personalized medicine, use of genome-coded information to prognosticate occurrence of diseases, an individual approach, and analysis of susceptibility to some therapy. Though not all HGP expectations have become a reality, the research activity aimed at ethical, legal and social effects or aspects (ELSI and ELSA respectively) was a trend towards complexity, transformed approach to human examination, where philosophy accomplishes an integrative function. Such discipline as bioethics serves as an example. All the enumerated above was true for a relatively new branch named epigenetics. In spite of being frequently opposed to its 'elder sister', it inherits many features of socio-humanitarian expertise.

In a wider sense, epigenetics examined the inherited changes in gene expression not associated with the changed DNA sequence. The mechanisms of epigenetics commonly mean DNA methylation, modified histones and microRNA with every enumerated process having a unique dynamic pattern and can alter the genome function under the exogenous effect [2]. It is worth noting that during the last 20 years, epigenetics hasn't lost the relevance and also formed a special field of research, which can be characterized both as very promising, and controversial.

The term 'epigenetics' was first used by Conrad H. Waddington in 1942 to determine 'the mechanisms used by genes to induce phenotypical signs' [3]. The images of epigenetics have been significantly modified since that time due to development of molecular biology. It was transformed into a multi-faceted field of various trials, including examination of interrelations between the internal effect and DNA methylation, histone modifications, dependance of diseases on epigenetic options, and specific intergenerational inheritance of epigenetic mechanisms.

Scientific achievements in this area have attracted attention of different scientists and stakeholders with discussions at the medical, philosophical, legal and commercial levels. Positions regarding epigenetics are commonly divided into optimistic, the ones that consider a bunch of possibilities and advantages, which can be provided to the human being by such a discipline, neutral and cautious, which discuss potential risks associated with development and implementation of epigenetic technologies and its explanatory capabilities into different spheres of life.

Meanwhile, epigenetics is one of the brightest modern examples of the implementing trend towards inter- and transdisciplinarity, and uniting philosophers, doctors, sociologists, lawyers, anthropologists, etc. into one group. Epigenetics is considered as a possibility to unite isolated disciplines because the research object includes both cultural and biological context. It becomes a borderline link, suggesting that different methodology trends can have innovative forms of cooperation.

## REPRESENTATION OF EPIGENETICS IN MASS MEDIA AND SCIENCE

Perspectives and emotional content of epigenetics can be explained due to a breakthrough in the explanation of gene expression plasticity, comprehending how environmental factors can inheritably influence the phenotype, but not the genotype. Epigenetic trials undermine the 'gene-feature' and 'genotype-phenotype' rigid reductive structure, rejecting the gene causality with reference to such a feature of biological systems as emergence, i. e., ignoring the traits of separate portions or structural elements.

It is noteworthy that active development of this area for the last twenty years evoked a ready response and was widely covered in media [4]. Representation of the wide audience is built on the mentioned opposition to genetics. In the public discourse, the last is characterized as strictly determined, passive and not exposed to environmental effect, whereas epigenetics is represented as space for dynamics and even personal enhancement. The main feature that shaped such an opinion is reversibility of epigenetic changes and their dependence on the way of life and environment (with reference to the issue of determining the environment as it is). The two terms are defined in a vague and wide way, including 'everything around you', from ecological factors that influence the individual body to such behaviors as alcohol consumption, physical activity, smoking, nutrition, mental stress, sleep deprivation, constant stay in the sun, etc. [5]. The community is attracted by the biohacking potential of epigenetics described in mass media. Thus, it deprives us from the 'genetic destiny' and inheritance is no longer a prevailing factor of human life. In simplified forms, the methyl groups are expression ON/OFF switches, whereas histones are brightness ON/OFF switches. Mass media representation has a number of almost classical problems such as extremely concept oversimplifying (both on the part of genetics, and epigenetics), formation of wrong expectations and conclusions that occur due to arbitrary interpretation of the researchers. However, the image is rather homogenous and is built on the opposition to genetic determinism and biological destiny, partially exposing controversial elements and extrapolations present in the scientific environment.

Researchers have different opinions. They, however, have high expectations, too. Epigenetics stimulates development of epistemic challenges. This is explained by a possible effect of science achievements in this area at several levels, integrating the positivistic, structural and social approaches in the research.

On the one hand, epigenetics can be considered as an argument against genocentric deterministic theories. On the other hand, it can serve as a counterargument to assertion that culture has primacy over nature. Thus, it can't solve the classic 'nature-nurture' dichotomy in favor of one party. It, however, provides for better comprehension of the uneasy or totally lacking difference between nature and upbringing, and makes the concepts of 'joint manufacture' (theory of gene-culture coevolution) more relevant.

It is true that epigenetics considers a genome as a biosocial construct during the 'post-genomic era' [6], and turns the gene used to be treated as stable or unchanged into a more plastic and flexible substance.

The particular value of epigenetics consists in taking an epistemic turn involving reestimation of social and biological links, better comprehension and emphasizing the importance of the first one, explaining the complex interrelations. The discipline states that external sociocultural and ecological factors are internalized into the body functioning by way of forming long-term biochemical changes.

These mechanisms can be conceptualized as a special human 'epigenetic history', embodiment of personal experience, surrounding reality, integrated at the molecular level. Being the new 'biologization' of sociocultural reality, it can be completely integrated into public discourses and practices. Knowing of epigenetic processes is a new focus on social and political space. Thus, epigenetic markers can be used as a proof of influencing social injustice in the past and subsequent life of a human being and descendants.

The position should, however, be taken with caution, as complex social processes reduced to biochemical processes can have a number of negative effects and support the deterministic thinking by means of epigenetics connection between epigenetic profiles and genotypes, their inheritance and, thus, influence on development of future generations.

## EPIGENETICS AS A VECTOR OF PREVENTIVE HEALTHCARE AND SOCIAL POLICY DEVELOPMENT

Epigenetics also promotes better understanding the sources of diseases and health factors. This allows to use it as an additional argument in favor of subsequent development of preventive social practices, including the ones in the area of healthcare. Some researchers know that shedding light in close interrelation of the human body and environment, epigenetics makes it possible to expand the scope of bioethics coverage and include the environmental issues, public healthcare and social conditions [7].

Apart from that, epigenetics shows how an early life experience influences gene expression later in life, gradually providing access to understanding the necessary conditions of health improvement in children of the future. From the commercial point of view, epigenetics provides additional

proof of importance of social workers, enhancing the prestige and financing of these professions. Thorough examination of health social determinants can significantly improve preventive medicine by preventing a wide spectrum of diseases, including mental health disorders. Potential inheritance of epigenetic regulation increases the relevance of epigenetics even more, because if harm produced by social disasters and toxic effect influences future generations, implementation of preventive public strategies becomes urgently prioritized.

New biologization of social space implemented by epigenetics can modify the ideas of functioning of the society and political movements [8]. It has been mentioned that epigenetics is used as evidence of influence produced by social injustice and poor ecology on the biological inequality among people and even generations. This inevitably results in discussion of the discipline value for theories of justice. Thus, some researchers challenge the opposition of traditional approaches by J. Rawls concentrated on socially induced differences in vital possibilities and egalitarian theories, which include congenital or inherited biological inequality, which unjustly reduce and worsen vital possibilities by birth. Casting light on the mechanisms used to bring social injustice to life and for its transfer to children, epigenetics rejects the 'social lottery', eliminating the boundaries between the two mentioned concepts and synthesizing them. The role of countries in prevention of epigenetic factors is increased in this regard.

On the one hand, it can be an additional argument in favor of the social justice concept, demonstrating discrimination of poor people. Moreover, some researches show the influence of early life experience on gene expression at a later age; this can enhance development and lobbying the advanced political preventive practices to eliminate the biological inequality, which, first, reduces the living possibilities soon after the birth and, second, can be inherited by other generations. On the other hand, considering complex social issues from the biological point of view can result in undesirable effects. Problems can arise during an attempt to determine the 'ideal' epigenomes because of high contextuality of the discourse. In this regard, epigenetics follows its 'elder sister', genetics. Complex determination of ideal or 'normal' genomes is followed by an equivalent issue assessing reference epigenomes, as it is not always possible to differentiate between epigenetic options leading to a higher risk of certain diseases and options which constitute a favorable biological adaptation to specific context of development at this very stage [9]. Irregularity and reversibility of epigenetic changes in different cells found during different periods of time hinder the analysis.

Thus, environmental conditions can be favorable for the entire population, but detrimental for a certain group. This brings up the question of the borders between the possible political intervention and epigenetic control. If epigenetic programming improves the individual adaptation to own context, the universal politicians can induce unintentional harm. Injustice is associated with a group membership, but not with epigenetic signs, which turn into shortcomings under certain conditions.

Moreover, the model of racial differences in health (prevalence of premature labor and cardiovascular diseases among African Americans) proposed by some researchers, generates a separate ethically problematic field as related to biological comparisons among any social groups. Epigenetic researches can provide a new idea of long-term effects of discrimination views, discourses, practices and social structures on health and well-being of certain populations. However, there is a risk of occurrence of reductionistic and fatalistic views on expression of genes, which, in its turn, gives birth to the view about the 'excessive' or critical epigenetic damage of some people. This makes related preventive social policies unsuccessful. The ideas can increase discrimination among groups of population, resulting in greater marginalization and stigmatization of certain groups. So, epigenetics can form a new basis for reproduction and consolidation of differences in the society and preserving biological inferiority of the poor or marginalized levels of the society.

In spite of what was mentioned above, it is worth noting that incorrect generalizations in the representation of epigenetics, especially within socio-humanistic disciplines, exaggerate the explanatory capacity of epigenetic mechanisms. The specific 'rhetoric of the future' displayed throughout the entire technocratic discourse and reliance upon prediction and control as the principal epistemic values promote instrumental conceptualization of epigenome and supply epigenetic factors with a unique discreteness, which can be misleading as well. The researchers should be careful about similar 'mythologization' of epigenetics.

## EPIGENETIC RESPONSIBILITY

Epigenetic responsibility, which is opposed to collective and individual moral responsibility for epigenetic health, stands as a separate issue [10]. This leads to discussion regarding how and when people can estimate their own epigenetic risks and risks for their children. Moreover, a question about assessment of epigenetic harm inflicted in the result of voluntary and conscious actions (which is a separate concern) was posed directly.

The metaethical issue of 'non-identity', which raises a question about the ethical preference of any action aimed at the future generations, is singled out specifically. It concerns epigenetic preconditions of birth and its unique environment. Epigenetic and genetic trials [11] display a specific temporality of conception and birth, unpredictable situation with a certain individual. Epigenetic responsibility of parents consequentially results in the ethical responsibility of all parents to reproduce the best offspring, follow the principle of reproductive benefit and partial negation of reproductive freedom, stigmatizing and depreciating the life of sick people. Not every life, but only the life with a certain degree of well-being, is worth living then. As a result, assessment of benefit and harm of existence is difficult.

Characteristics of both anti-deterministic or non-deterministic epigenetics can be hasty and incorrect, as it is based on simplification of epigenetics and genetics it is opposed to. The opposition consists in determination of the research language for this discipline. Apart from that, epigenetic determinism can be considered in some cases, for instance, perinatal or pediatric effect can be called as predetermined as separate genes. In its turn, epigenetic determinism can result in discussion of confidential data about epigenome, similar to debates on the access to genetic data. Some epigenetic data can be of great concern, as they present information not just about the risks of current diseases, but also about the previous way of life. So, microRNA expression profiles found in the blood can be compared to a certain individual with a probability of 90% [12]. This can result in effects that will prevent researches and medical practice.

Use of epigenetics in law is of note as well. It can enable tracing the harm due to the effect of chemical substances. Here, 2 issues arise: first, qualitative assessment of the rate of epigenetic harm is difficult; second, the latent time until occurrence of exposure symptoms can exceed the period of limitations. Development of long-term neurological and mental

effects of epigenetic harm can still result in reinterpretation of criminal responsibility.

Certainly, epigenetics influences the reproductive sphere. Thus, the area of 'maternal effect' is being expanded; not just the reproductive period, but also lives of mothers prior to childbearing is analyzed, which is interpreted with some caution, as the maternal body considered as the 'epigenetic vector' can intensify control over women. The assisted reproductive technologies and surrogate maternity, which influence the epigenetic programming and health of future children, are considered as well. Thus, the ethical issue about the controversy between the reduced risk of congenital diseases, abnormalities and reproductive autonomy has been raised.

## CONCLUSION

In the future, epigenetic testing can open up new possibilities for personalized medicine, enabling to use epigenetic markers for more effective early detection, diagnostics and prognostication of diseases including cancer, cardiovascular, respiratory and neurogenerative diseases, and individual selection of the most effective medications that involve epigenetic mechanisms (pharmacoepigenetics) [13].

Thus, the value of epigenetics for public well-being and health can't be overestimated, as the discipline is still in an embryonic stage. Unconditional proof of an epigenetic trial in humans is currently lacking. It is necessary to solve a very important metaethical issue regarding prescriptive and standardized value of epigenetics empirical data.

Considering all the above, a number of basic issues of epigenetic trials for socio-humanitarian disciplines can be mentioned [14]:

1. Nature-nurture dichotomy.
2. Biologization of social space.
3. Public healthcare and preventive strategies.
4. Reproductive policy and parental responsibility.
5. Political theory (theory of justice in particular).
6. Stigmatization and neoeugenics.
7. Confidentiality protection.
8. Legal advice.

The exceptionality of epigenetics postulated by some researchers doesn't prove itself, as epigenetics discourse is rather an important extension of ideas that have already been spread in genetics. The area of research is a typical example of the growing trend towards the new synthesis of human interdisciplinary research and overcoming reduction in the process of comprehension, with an important role being played by philosophy and bioethics, in particular [15]. The author also sincerely hopes for subsequent development of these problematic fields, especially by the Russian researchers, as the socio-humanitarian concerns of epigenetics are poorly highlighted in Russian literature. Development of potential effects of epigenetic trials can add to and enhance ideas of ethical, social and legal theories.

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