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.

References

1. WHO expert advisory committee on developing global standards for governance and oversight of human genome editing: report of the sixth meeting. Available from URL: https://www.who.int/publications/i/item/who-expert-advisory-committee-on-developing-global-standards-for-governance-and-oversight-of-human-genome-editing-report-of-the-sixth-meeting.
2. Park S, and Beal PA. Off-target editing by crispr-guided dna base editors. Biochemistry. 2019; 58: 3727–3734. DOI: 10.1021/acs.biochem.9b00573
3. Zhang X-H, Tee, L Y, Wang X-G, Huang Q-S, and Yang S-H. Off-target effects in crispr/cas9-mediated genome engineering. Mol Ther Nucleic Acids. 201; 4: e264. DOI: 10.1038/mtna.2015.37
4. Biesecker LG, and Spinner NB. A genomic view of mosaicism and human disease. Nat Rev Genet. 2013; 14: 307–320. DOI: 10.1038/nrg3424
5. Archer NM, Petersen N, Clark MA, Buckee CO, Childs LM, and Duraisingh MT. Resistance to plasmodium falciparum in sickle cell trait erythrocytes is driven by oxygen-dependent growth inhibition. Proc Natl Acad Sci U. S.A. 2018; 115: 7350–7355. DOI: 10.1073/pnas.1804388115
6. Baylis F, Darnovsky M, Hasson K, and Krahn TM. Human germline and heritable genome editing: the global policy landscape. CRISPR J. 2020; 3: 365–377. DOI: 10.1089/crispr.2020.0082
7. Macintosh KL. Heritable genome editing and the downsides of a global moratorium. CRISPR J. 2019; 2: 272–279. DOI: 10.1089/crispr.2019.0016
8. Helicos went bankrupt in 2012 and SeqLL bought all its intellectual property and hardware // http://seqll.com
9. Konig H. Germline-editing moratorium — why we should resist it. Nature. 2019; 458 p. DOI: 10.1038/d41586–019–01292–6
10. Lander ES, Baylis F, Zhang F, Charpentier E, Berg P, Bourgain C, et al. Adopt a moratorium on heritable genome editing. Nature. 2019; 567: 165–168. DOI: 10.1038/d41586–019–00726–5
11. Normile D. Shock greets claim of crispr-edited babies. Science. 2018; 362: 978–979. DOI: 10.1126/science.362.6418.978
12. Cyranoski D. What crispr-baby prison sentences mean for research. Nature. 2020; 577: 154–155. DOI: 10.1038/d41586–020–00001-y
13. Joy MT, Assayag EB, Shabashov-Stone D, Liraz-Zaltsman S, Mazzitelli J, Arenas M, et al. Ccr5 is a therapeutic target for recovery after stroke and traumatic brain injury. Cell. 2019;176: 1143–1157.e13. DOI: 10.1016/j.cell.2019.01.044
14. Fletcher JC, and Anderson WF. Germ-line gene therapy: a new stage of debate. Law Med Health Care. 1992; 20: 26–39. DOI: 10.1111/j.1748–720X.1992.tb01171.x
15. Wilholt T. Die Freiheit Der Forschung: Begründungen Und Begrenzungen. Berlin: Suhrkamp, 2012.
16. The protection of the human embryo in vitro. Report by the Working Party on the Protection of the Human Embryo and Fetus (CDBI-CO-GT3). Available from URL: http://www.coe.int/t/dg3/healthbioethic/activities/04_human_embryo_and_foetus_en/GT3%20(2003)13%20.
17. Brinegar K, Yetisen AK, Choi S, Vallillo E, Ruiz-Esparza GU, Prabhakar A M, et al. The commercialization of genome-editing technologies. Crit Rev Biotechnol. 2017; 37: 924–932. DOI: 10.1080/07388551.2016.1271768
18. Thompson DF. Understanding financial conflicts of interest. N Engl J Med. 1993; 329: 573–576. DOI: 10.1056/NEJM199308193290812
19. Lieb K, Klemperer D, Kolbel R, and Ludwig W-D, (eds.). Interessenkonflikte, Korruption und Compliance im Gesundheitswesen. Berlin: Medizinisch Wissenschaftliche Buchgesellschaft, 2018.
20. Krimsky S. Conflicts of Interest in Science: How Corporate-Funded Academic Research Can Threaten Public Health. New York: Skyhorse, 2018.
21. Mahla RS. Stem cells applications in regenerative medicine and disease therapeutics. Int J Cell Biol. 2016; 1–24. DOI: 10.1155/2016/6940283
22. Dollars for Profs. Dig Into University Researchers' Outside Income and Conflicts of Interest By Sisi Wei, Annie Waldman and David Armstrong, ProPublica. Published December 6, 2019. Available from URL: https://projects.propublica.org/dollars-for-profs

Литература

1. WHO expert advisory committee on developing global standards for governance and oversight of human genome editing: report of the sixth meeting. Режим доступа: [Электронный ресурс]. URL: https://www.who.int/publications/i/item/who-expert-advisory-committee-on-developing-global-standards-for-governance-and-oversight-of-human-genome-editing-report-of-the-sixth-meeting.
2. Park S, and Beal PA. Off-target editing by crispr-guided dna base editors. Biochemistry. 2019; 58: 3727–3734. DOI: 10.1021/acs.biochem.9b00573
3. Zhang X-H, Tee, L Y, Wang X-G, Huang Q-S, and Yang S-H. Off-target effects in crispr/cas9-mediated genome engineering. Mol Ther Nucleic Acids. 201; 4: e264. DOI: 10.1038/mtna.2015.37
4. Biesecker LG, and Spinner NB. A genomic view of mosaicism and human disease. Nat Rev Genet. 2013; 14: 307–320. DOI: 10.1038/nrg3424
5. Archer NM, Petersen N, Clark MA, Buckee CO, Childs LM, and Duraisingh MT. Resistance to plasmodium falciparum in sickle cell trait erythrocytes is driven by oxygen-dependent growth inhibition. Proc Natl Acad Sci U. S.A. 2018; 115: 7350–7355. DOI: 10.1073/pnas.1804388115
6. Baylis F, Darnovsky M, Hasson K, and Krahn TM. Human germline and heritable genome editing: the global policy landscape. CRISPR J. 2020; 3: 365–377. DOI: 10.1089/crispr.2020.0082
7. Macintosh KL. Heritable genome editing and the downsides of a global moratorium. CRISPR J. 2019; 2: 272–279. DOI: 10.1089/crispr.2019.0016
8. Helicos went bankrupt in 2012 and SeqLL bought all its intellectual property and hardware // http://seqll.com
9. Konig H. Germline-editing moratorium — why we should resist it. Nature. 2019; 458 p. DOI: 10.1038/d41586–019–01292–6
10. Lander ES, Baylis F, Zhang F, Charpentier E, Berg P, Bourgain C, et al. Adopt a moratorium on heritable genome editing. Nature. 2019; 567: 165–168. DOI: 10.1038/d41586–019–00726–5
11. Normile D. Shock greets claim of crispr-edited babies. Science. 2018; 362: 978–979. DOI: 10.1126/science.362.6418.978
12. Cyranoski D. What crispr-baby prison sentences mean for research. Nature. 2020; 577: 154–155. DOI: 10.1038/d41586–020–00001-y
13. Joy MT, Assayag EB, Shabashov-Stone D, Liraz-Zaltsman S, Mazzitelli J, Arenas M, et al. Ccr5 is a therapeutic target for recovery after stroke and traumatic brain injury. Cell. 2019;176: 1143–1157.e13. DOI: 10.1016/j.cell.2019.01.044
14. Fletcher JC, and Anderson WF. Germ-line gene therapy: a new stage of debate. Law Med Health Care. 1992; 20: 26–39. DOI: 10.1111/j.1748–720X.1992.tb01171.x
15. Wilholt T. Die Freiheit Der Forschung: Begründungen Und Begrenzungen. Berlin: Suhrkamp, 2012.
16. The protection of the human embryo in vitro. Report by the Working Party on the Protection of the Human Embryo and Fetus (CDBI-CO-GT3). Режим доступа: [Электронный ресурс]. URL: http://www.coe.int/t/dg3/healthbioethic/activities/04_human_embryo_and_foetus_en/GT3%20(2003)13%20.
17. Brinegar K, Yetisen AK, Choi S, Vallillo E, Ruiz-Esparza GU, Prabhakar A M, et al. The commercialization of genome-editing technologies. Crit Rev Biotechnol. 2017; 37: 924–932. DOI: 10.1080/07388551.2016.1271768
18. Thompson DF. Understanding financial conflicts of interest. N Engl J Med. 1993; 329: 573–576. DOI: 10.1056/NEJM199308193290812
19. Lieb K, Klemperer D, Kolbel R, and Ludwig W-D, (eds.). Interessenkonflikte, Korruption und Compliance im Gesundheitswesen. Berlin: Medizinisch Wissenschaftliche Buchgesellschaft, 2018.
20. Krimsky S. Conflicts of Interest in Science: How Corporate-Funded Academic Research Can Threaten Public Health. New York: Skyhorse, 2018.
21. Mahla RS. Stem cells applications in regenerative medicine and disease therapeutics. Int J Cell Biol. 2016; 1–24. DOI: 10.1155/2016/6940283
22. Dollars for Profs. Dig Into University Researchers' Outside Income and Conflicts of Interest By Sisi Wei, Annie Waldman and David Armstrong, ProPublica. Published December 6, 2019. Режим доступа: [Электронный ресурс]. URL: https://projects.propublica.org/dollars-for-profs