PERSPECTIVE

Bioethical and Legal Issues in 3D Bioprinting

Anastasia Kirillova[1,†,*], Stanislav Bushev[2,†], Aydar Abubakirov[1], Gennady Sukikh[1]

[1]National Medical Research Center for Obstetrics, Gynecology and Perinatology Named After Academician V.I. Kulakov of the Ministry of Healthcare of Russian Federation, Moscow, 117513, Russia

[2]Department of Philosophy, Lomonosov Moscow State University, Moscow, 119991, Russia

[†]These authors contributed equally to this work.

Abstract: Bioethical and legal issues of three-dimensional (3D) bioprinting as the emerging field of biotechnology have not yet been widely discussed among bioethicists around the world, including Russia. The scope of 3D bioprinting includes not only the issues of the advanced technologies of human tissues and organs printing but also raises a whole layer of interdisciplinary problems of modern science, technology, bioethics, and philosophy. This article addresses the ethical and legal issues of bioprinting of artificial human organs.

Keywords: Three-dimensional printing, Bioethics, Ethical issues, Regulatory concerns, Artificial ovary, Oncofertility

***Corresponding Author:** Anastasia Kirillova, National Medical Research Center for Obstetrics, Gynecology and Perinatology Named After Academician V.I. Kulakov of the Ministry of Healthcare of Russian Federation, Moscow, 117513, Russia; stasia.kozyreva@gmail.com

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1 Introduction

Three-dimensional (3D) bioprinting of tissue-engineered constructs and prototype organs for regenerative medicine is one of the most rapidly developing and promising areas of biotechnology. There are already more than a dozen leading companies in medical bioprinting: EnvsionTEC (Germany), RegenHu (Switzerland), Poetis (France), Organovo (USA), Sciperio/nScript (USA), Cellink (Sweden/USA), Allevi (formerly BioBots) (USA), BioDevices (USA), three Dynamics systems (USA), Aspect Biosystems (Canada), Rokit (South Korea), 3D Bioprinting Solutions (Russia), etc.[1]. The development of 3D bioprinting technologies has even been called the megatrend of the fourth industrial revolution[2].

To date, the development of bioprinting technology completed the first stage, which can be called the stage of "apologetics," when doubts about the possibility of implementing bioprinting have been dispelled, successes of using the technology for bioprinting tissues and organs have been demonstrated, basic techniques and methods have been worked out, and a number of technical restrictions for implementing the technology have been overcome. The latest advances in bioprinting technologies and biofabrication approaches are indeed impressive. Since the pioneering work of organ printing[3], the scientific community of biofabrication has been developed, uniting biologists, medical doctors, physicists, chemists, and computer scientists[4]. Although the technology progressed very fast, on the onset of its development the possibility of functional human organ bioprinting seemed like a highly desirable, yet a long-term, and goal[4]. Now, decades later with the successes in

human[5-7] and animal models[8-10] bioprinting, we became much closer to the ultimate goal.

Now comes the next stage, which can be called the stage of "evangelism" which is the demonstration of the possibilities of bioprinting application for solving a number of problems in medicine. The bioprinting approach has already been used to address problems in transplantology, regenerative medicine, and even in the field of reproduction. Printed tissues are used in experimental pharmacology research for drugs and toxicity testing and in cosmetology[11,12]. Naturally, the prospect of replacing diseased organs with healthy ones can be interpreted as a weal. It can not only solve the issue of organ and tissue shortage for transplantation but can also overcome a number of ethical problems related to transplantation. The bioprinting technologies can also contribute to the emergence of a new paradigm in medicine – personalized medicine[13], including personalized drug delivery[14]. Successes in the field of bioprinting announce the promising possibility for replacing bones, cartilage, blood vessels, and internal organs (heart, kidneys, liver, etc.) in humans. Research is underway in the field of reproductive medicine using bioprinting technologies, in particular, the biofabrication of artificial ovaries[15-18].

However, as for every new technology, the ethical and legal norms of 3D bioprinting will have a long way until they establish. In this work, we will address the ethical and legal problems of human organ 3D bioprinting. We will highlight the issues of artificial ovary biofabrication, as this unique technology concerns not only patients' health but also the health and well-being of future offspring. In the end, we will formulate a number of recommendations for the regulation of this field of scientific research and medical practice in the future.

2 Bioethical and legal issues of 3D bioprinting

2.1 Current and possible directions of bioethical discussions related to the emergence and development of 3D-bioprinting

The development of bioprinting technologies raises deep questions related to the very human nature, biotechnological projects of "human enhancement"[19], the issues of "technological design"[20] youth extension, and even "technological immortality" of a human being. "Technological immortality" programs can be divided into two groups: Rejuvenation technologies (stopping the aging program) and consciousness transfer technology (unloading of the human personality). New organs bioprinting and replacing the old organs with them belongs to the rejuvenation technologies[21] which raises the question of indications and limits of application of bioprinting technologies.

One of the first issues related to the development of organs and tissues bioprinting is the question of the feasibility of developing these technologies and the moral validity of it. Why and for what purpose are we ready to print organs? The answer seems obvious, based on the need for organ transplantation, the shortage of organ donation around the world. The development of technology can help save the lives of a very large number of people. The majority of governmental and international organizations now see this technology as morally justified if it has a therapeutic effect. As G. B. Yudin observes: "The main platform for justifying the widespread use of biotechnology is provided by the utilitarian philosophy." Undoubtedly, there are gradations here – from radical transhumanism, which recognizes no limits for technological improvement of a human being (human enhancement), to more cautious versions, which recognize the social risks of human change. In general, however, the utilitarian framework of ethical thought is more inclined to protect human modification projects as they are driven by the individual's desire for self-improvement and a better life[22]. The scope of medical biotechnologies is becoming wider and increasingly blurred, and it is already difficult to distinguish between therapy and human improvement[23]. It is also very important to pay attention to the speed at which these technologies develop to identify and study ethical problems before a therapeutic 3D bioprinting is ready for widespread use in patients[24].

3D bioprinting deserves special attention as the utilization of viable cells in the printing process creates particular ethical and regulatory

problems[24,25]. The "cell" is the most important component of bioprinting. The type of cells used plays a key role in determining the characteristics of the bioprinted tissue. In the case of allogeneic cell transplantation, we face classical ethical problems associated with donation: (1) The donor confidentiality, (2) the informed donor consent, (3) the possible invasive cell production procedure, and (4) donor cell ownership. There is still no verdict among clinicians and researchers regarding one of the basic rules of medical ethics – *Primum non nocere* (First, do no harm). The principle of misuse takes into account the moral nature of the action, the intention of the agent, the means of action, the possible adverse effects, and the proportionality between good and bad effects.

Stem cells are often used as "building blocks" for human tissue and organ biofabrication. The main ethical issue with regard to stem cells is its "source." The use of human embryonic stem cells (ESCs) has been heavily criticized and has relevant limitations, both legal[26,27] and moral[28,29]. The main source of these cells are embryos or fetuses, so the problem of obtaining ESC is at the intersection of bioethical problems of determining the moral status of an embryo, legal pregnancy termination, and human participation in the experiments. In addition to the ethical and legal issues associated with the use of ESCs, other factors may influence the ethical acceptability of using bioinks from allogeneic cells. For instance, the issues of obtaining stem cells from donors who have been pressured, coerced, or have not given informed consent should be taken into consideration. Moreover, there are barriers for commercialization and therefore, the application of 3D printing technology on the basis of ESC as "use of human embryos in industrial and commercial purposes cannot be the objects for patent rights" according to the subclause 3 of Clause 4 of Article 1349 of the Civil Code of the Russian Federation.

Another option for the cell source for bioprinting is xenogeneic cells. In this case, it is necessary to take into consideration the social and religious aspects of animal cell utilization. Patients with xenotransplantation might experience psychosocial problems associated with their personal identity[30]. Moreover, patients with religious beliefs may disagree with the use of cells of certain animal species.

The emerging possibilities of reprogramming differentiated cells and producing induced pluripotent stem cells (iPSCs) eliminate the ethical issues of using ESCs or xenogeneic cells. IPSCs can be purposefully differentiated into any specific adult body cell types, ranging from skin cells to cardiac cells and neurons. However, we believe that the technology of 3D printing of human organs using autologous iPSC in bioink is not ethically neutral. It also has a number of problematic aspects, even if the bioinks are derived from the patient's own cells. The technology of cell reprogramming is also very far from perfect. Today, one of the main challenges is to develop the methods that will ensure correct differentiation of all stem cells before transplantation. The risk of tumorigenicity is a major problem when using iPSC[31-33]. To provide safety of iPSC-based therapies, genetic testing of stem cell lines potentially suitable for clinical application has to be performed[34-36]. However, it brings additional ethical and legal issues related to the personal genetic information collection, storage, and use.

Data exchange for research purposes increases the number of individuals who can access personal genomic data which, in turn, increases the likelihood of data leakage and its malicious use, including for the purpose of committing a crime. In 2012, The Presidential Commission for the Study of Bioethical Issues published "Privacy and Progress in Whole Genome sequencing" report in the United States[37]. This report gives recommendations for individual's privacy protection while allowing exchanging genetic data. The Russian legislation does not regulate the organization and conducts of research related to human genome data and activities of the relevant genetic companies. Requirements for obtaining consent from a donor for participation in research, as well as requirements for the processing and transfer of genetic information as a special category of personal data, are not defined in the existing legislation. Additionally, current legislation does not regulate the circulation of biological materials seized from donors for the purpose of conducting scientific research, does not provide guarantees of

protection rights of donors, and does not stipulate the mandatory procedure for the preliminary approval of research by ethical committees[38,39].

Another aspect that needs to be taken into consideration while evaluating the ethics of bioprinting is that the technology is set by a digital model. A number of authors note that the development of 3D bioprinting technology leads to the "digitalization" of objects of the material world, the boundaries between the physical world and the digital space erase, and bioprinting starts to digitize the person himself[40,41]. The printed organs which are biofabricated on the basis of digital models will replace the natural ones, and thus, models will replace nature. Therefore, a question of responsibility for the development and evaluation of the 3D models arises: who and to which extent shall be responsibile for the translation of the anatomical image into digital - «designers», biologists, or programmers? Who will have the legal rights for the model? Will it be possible to use the model without a patient's consent? Is it possible to apply the models commercially? The questions of confidentiality and privacy arise regarding human digitization. In the case of bioprinting technology, the digital 3D model will represent personalized human data. Such information needs to be considered private, and special rules regulating the receipt, storage, handling, processing, and application of such information are required.

The two fundamental principles of human rights protection in the field of biomedical research are the principle of informed consent and the principle of confidentiality. The principle of confidentiality is closely related to the notion of "medical secrecy" and implies that the circumstances of treatment and the patient's characteristics are kept confidential with the respect to the patient's life. Confidentiality helps to build trust relationships that are essential for effective and timely medical care. The principle of informed consent is also one of the main in the system of ethical and legal support of medical activity[42,43]. It derives from the concept of general human rights and is, therefore, generally accepted and allocated in a number of international and national documentations. For example, the Nuremberg Code provides for absolute voluntary consent for human participation in medical trials including knowledge of the nature, duration, and purpose of the experiment, its methods, and associated risks. According to the Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (ETS No. 164), medical intervention can be performed only after the person gives his/her voluntary written consent based on the information received on the purpose and nature of the intervention, as well as its consequences and risk. In 3D bioprinting, problems might arise in case of obtaining informed consent in emergency situations where a patient is unable to express informed consent. Obtaining informed consent can also be challenged in situations where a participant does not have the full ability to make a donation decision (e.g., some patients may be in intensive care units)[24].

To introduce the 3D bioprinting technology into clinical practice and eliminate the associated risks, clinical trials are required. Along with the known ethical rules and standards for conducting experimental procedures involving humans, in the case of 3D bioprinting of human tissues and organs, specific issues arise regarding the design of human clinical trials[24]. As 3D bioprinting technology develops within the personalized medicine paradigm[13,20], each biofabricated product is individually tailored for a particular person and might require additional modifications to the experiment design in each case. Thus, standard approaches for clinical trials such as double-blind randomized control studies cannot be applied to 3D bioprinting technology. Each 3D bioprinted treatment is unique and adapted to a specific individual taking into consideration only his or her conditions, and therefore, results of each case cannot be fully extrapolated into future treatments. Nevertheless, while the biomaterials are personalized, criteria and protocols for the procedures can be standardized based on the first clinical trials. The organization of the experimental studies on human organ 3D bioprinting is a challenging task. The study has to be ethically

acceptable and safe for the patients. The efficiency and safety of the custom-made organs cannot be tested on other individuals; therefore, in this respect; each patient becomes the first examinee. Consequently, the question arises of the ratio of risks to benefits, criteria of inclusion, for instance, the participation of terminally ill patients in experiments.

Another issue concerning clinical studies of 3D bioprinting-assisted treatments is the question of study termination by a participant. Unlike standard clinical trials, for example, when drug dosage can be gradually adjusted, patients involved in a 3D printing trial may have difficulties with exercising their right to withdraw from the trial after implantation of an artificial organ. Interventions in 3D bioprinting treatments might be limited in terms of procedure reversibility (removal of the implant and all cells that have grown out of it) and the attempts of reverse implantation might lead to further harm to patients. Most importantly, a patient might lose a chance for an alternative treatment due to participation in a bioprinting trial[24].

2.2 Legal issues of 3D bioprinting and introduction into clinical practice

Legal and government institutions around the world define the legal regulation of 3D bioprinting as a complex problem with no generally accepted satisfactory solutions for addressing the potential and uncertain risks of harm. The issues become even more exacerbated as numerous participants are involved in the production chain of bioprinting. Expertise from 3D model designers, medical professionals, lawyers, engineers, biologists, members of the ethical committee, and insurance companies are necessary for multi-stakeholder collaboration to form an acceptable path for the bioprinting technology development and introduction into clinical practice. There is currently no *sui generis* regulatory regime governing the entire bioprinting process, but there is partial legislation concerning tissue engineering and regenerative medicine.

According to the European Commission (EC) and European Medicines Agency gene therapies, somatic cell therapies and tissue engineered products are called advanced therapy medicinal products (ATMPs)[44]. The principles developed in the ATMPs Regulations of the EC might be applied to different stages of 3D bioprinting production. The key aspects of bioprinting management include the risks regulation and responsibility for product quality[45]. In this regard, the following issues may be very important: Who is primarily responsible for the quality of bioprinted products – the 3D bioprinting providers or medical organizations; who should be responsible for quality control; who should be liable in case of bioprinted organ quality claims from the recipient; etc.

Legal problems of creation and use of bioprinting human organs, discussion of a possible model of legal regulation of bioprinting technologies received special consideration in Russia[41,46,47]. The absence of norms in Russian legislation that regulates in the area of creation and implantation of bioprinted human organs is proposed to be a deterrent factor of 3D bioprinting technologies development[41]. Current revision of the Federal law dated 23.06.2016 No. 180-FZ "On biomedical cellular products" for the time being cannot regulate the utilization of biofabricated human organ, as this law does not govern organ transplantation issues. At the same time, the Law of the Russian Federation dated 22.12.1992 No. 4180-1 "On human organs and (or) tissue transplantation" can neither regulate the use of 3D printed organs, as 3D bioprinted products are artificial[41,48].

At present, the relations between 3D bioprinting providers, medical organizations, and patients can be settled down in the contract for works or medical services contract[46]. Such types of contracts can be used in case of personalized biofabrication of organs or tissues for an individual order. However, if bioprinted organs are depersonalized, then the sale-purchase agreement can be applied[46].

It also seems permissible for some specialists to "commercialize" the products in the field of bioprinting, as the final product of tissue engineering is so far from its original source (human biomaterial), that is, why the turnover of such products cannot be considered as

commercialization of the human body or its individual parts[41]. Bioprinted human organs have objective features that distinguish them from human organs. Biofabricated organs are created artificially, and the creative process is purposeful and controlled. They are formed outside of the human body and there are no significant risks to life and health of the cell donor during the biofabrication of artificial organs. Moreover, the informed consent concerns only the production of biological material, but not biofabrication of the organ itself[47]. These particular traits of 3D bioprinted organs before their transplantation to the human body might allow them to relate to objects of civil rights. As a result, the assumption of limited commercialization of the creation and utilization of biofabricated organs might be permitted[47]. However, after implantation of organs and tissues, they should be recognized as an integral part of a human body. Therefore, it is necessary to recognize the legal death of this organ as an object with the termination of the title of ownership and with the corresponding prohibitions and restrictions on their removal and subsequent sale, which exist with regard to the human biomaterial today[46].

The scope of legal regulation of 3D bioprinting action also includes a wide range of intellectual property rights, including patents, copyrights, design rights, and trademarks. Government intervention in research and new technologies development is essential because it will determine the future of technology. The political resolutions must be determined and corresponded normative issues must be addressed at the earliest stages of technological development. 3D bioprinting technology can save lives and revolutionize the medical sphere. Therefore, it deserves special attention and development of an appropriate legal framework[49].

2.3 Ethical issues of artificial ovary 3D bioprinting and introduction into clinical practice

Among organ bioprinting, biofabrication of reproductive organs stay apart as the need for transplantation of artificial ovaries, testes, and uteruses is not directly related to the threat of life, but to perceptions of the quality of life. Gonadotoxic oncological treatment can result in primary ovarian insufficiency in women of reproductive age. Therefore, different methods of fertility preservation (such as oocytes, embryos, and ovarian tissue cryopreservation) have been developed[50]. Unfortunately, there are currently no options for fertility restoration after remission for the group of patients with ovarian cancer or types of cancer metastasizing into the ovaries (such as leukemia, neuroblastoma, and Burkitt lymphoma)[16]. After the ovariectomy or the gonadotoxic oncological treatment, these patients suffer from irretrievable loss of reproductive and ovarian endocrine function. The development of artificial ovary technology gives hope to this group of patients for fertility preservation and the birth of genetically-related children. Such technology is currently under development, and the first successful animal experiments are known[9]. Human clinical trials are still far away, however at this stage of technology development, it is of high importance to identify and solve several important ethical and regulatory issues associated with artificial ovary 3D bioprinting.

Along with the ethical and legal issues of 3D bioprinting technologies discussed above, the bioprinted ovary project addresses issues related to human reproduction. First and foremost, the major ethical issue related to the development of a 3D bioprinted ovary project is the question of the risk-benefit ratio. Ovariectomy and gonadotoxic chemo- and radio-therapies, as oncological treatments are necessary procedures for patient's life preservation and therefore can be considered as the good. However, loss of reproductive function is a harm, and if there is an opportunity to correct it following the principle of *primum non nocere* and restore reproductive function, then it will be possible to compensate for the caused harm. It is a strong argument in favor of developing artificial ovary technology, but a number of profound conditions should be taken into consideration.

The risks associated with transplantation of 3D printed artificial ovaries should be clinically assessed as minimal. Therefore, all the possible

risks should be evaluated at each step of technology: Starting with bioinks creation and ending with organ transplantation. The particular and highly important feature of the artificial ovary technology is that the risks concern not only the patient herself but also the future offspring. The major concern is that *ex vivo* manipulations with ovarian follicles might lead to genetic and epigenetic changes in the egg cells which will directly affect the offspring's health. Moreover, quite often malignant diseases are hereditary. Thus, the artificial ovary technology would contribute to the transmission of genetic variants, associated with cancer to the next generations and therefore will artificially increase the percentage of patients with cancer. Another question that may arise with the artificial ovary technology implementation is the right to receive information about the birth of children. Can the information of conception with the assistance of artificial ovary 3D printing technology be traumatic to a child? Can it lead to a new form of stigmatization in society in the future?

Another important aspect of development and introduction into the clinical practice the ovary bioprinting technology is that several years have to pass from the moment of ovary removal to the moment of the possibility of artificial ovary transplantation due to oncological treatment. A patient might refuse transplantation when the organ is printed, but the use of such an expensive technology might emotionally pressure and oblige a patient to motherhood. The problem of voluntary rejection of transplantation in the case when an artificial organ is already printed raises both ethical and legal questions of ownership of printed organs. The same question is relevant in case of a patient's death. Can an artificial ovary be donated for scientific research or pharmaceutical drug testing?

The next equally important issue involved in the development of bioprinted ovary is the aspect of technology commercialization and the associated moral issue. The legislation of Russia allows commercial relations in assisted reproductive technologies. For instance, *in vitro* fertilization (IVF) can be provided in clinics on a paid basis. However, commercial relations in transplantation are prohibited by law in Russia. For example, the prohibition of organ sale is in conformity with the basic law of moral relations between people. The trend toward the commercialization of organ transplantation has its own objective reasons. One of the main reasons is the shortage of organs for transplantation, which forces patients to find extraordinary sources of donor organs. With the help of 3D printing technology, the problem of donor organ shortage can be solved, but an issue of the accessibility of technology to the entire population will arise. It is clear that the rich will be able to take advantage of 3D bioprinting, which will further widen the gap between the possessing classes and the indigent in our society. In the case of commercial creation and transplantation of artificial ovaries, this expensive scientific and technical solution can benefit only few members of a certain group, bringing an ethical problem of social stratification of bioprinting[51].

A number of questions arise regarding the inclusion criteria for artificial ovary technology implementation. Should there be an age limit for the use of technology? If a patient already has children, should artificial ovary transplantation be allowed? Can a woman with artificial ovaries participate in IVF programs? How can the presence of an artificial ovary affect the physical and mental integrity of a patient? If the ultimate goal of live birth is not achieved, how the responsibility will be distributed among programmers, engineers, biologists, and doctors? Should the state finance the production and transplantation of artificial ovary to its underprivileged, low-income citizens?

3 Conclusions and perspectives

As it is easy to see, there are more questions than answers in the area of bioethical and legal issues of 3D bioprinting. The lack of answers is due to the fact that the speed of development of research and the increase of technological capabilities largely outstrips the speed of our understanding of the moral and legal consequences of their development. Currently in Russia and globally, there is neither suitable statutory framework nor special regulatory guidelines governing 3D bioprinting of tissues and organs and their further

transplantation. The problem of ethical evaluation and legal regulation of 3D bioprinting are that this technology cannot be thoroughly evaluated using standard clinical trials or taking into account the current regulatory requirements.

However, before the 3D bioprinting technology spreads and becomes clinically available, several regulations of scientific research and medical practice should be adopted. First of all, there is a need to develop informed consents for donation, material manipulation, storage, and its further use, including for commercial and research purposes. Moreover, it is necessary to develop requirements for safety, quality, and efficiency of technological procedures and the end products obtained by 3D bioprinting taking into account the human rights and dignity. Furthermore, it is of great importance to establish committees for creation and regulation of national guidelines on technical, legal, and ethical issues related to the development and application of 3D bioprinting technologies. All patients including minors and incapable people need to be legally protected. Last but not least, it is essential to establish regulations of turnover and limits of commercialization for 3D bioprinting technologies of human organs and tissues, as well as possible sanctions for illegal trafficking of artificial organs.

Authors' contributions

Conception and design: AK and GS; Collection and assembly of data: AK, SB, and AA; Data analysis and interpretation: SB, AK, and AA; Manuscript writing: SB and AK; Final approval of manuscript: All authors.

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Conflicts of interest

No conflicts of interest are reported by the authors.

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