3D bioprinting: current social, ethical and legal aspects

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Abstract

3D bioprinting has become one of the most anticipated technologies in the medical and scientific world. This technology could help overcome the lack of organ transplants, including for the heart. It may soon become possible to 3D bioprint immunocompatibile and patient-specific tissue on demand at the time of need. However, the rapid pace of development of this new frontier in regenerative medicine threatens to outstrip the ethical and regulatory considerations which accompany it. This paper explores these new ethico-legal concerns. Aspects analysed include exaggerated results, inflated public expectations, the influence of social media and how the current ethical climate may foster suboptimal standards of conduct by researchers or companies We discuss the socio-cultural and religious overlays influencing the field and current socio-ethical challenges. The technical progress is only as strong as the maturity of the bioethical and regulatory framework in which it flows within which it develops.

Keywords: 3D bioprinting, tissue engineering, biomedical cell product, regenerative medicine, cardiac regeneration, transplantation, ethics, legal regulation. regulation

Introduction

Every human life has value and saving life is one of the key objectives of medical science. This is perhaps especially true in transplantation which has recently achieved astonishing success since successful transplantation of not only human organs such as the kidneys, liver, lungs, etc., but even the transplantation of the heart. According to Australian Donation and Transplantation Activity Report, in Australia during 2017 the number of organ transplant recipients was 1,402 Australians[1].

However, a common global problem is a constantly increasing number of patients requiring organ transplants and the lack of donor organs for transplantation. Thus, according to the Global Observation on Donation and Transplantation, in 2017, 139,024 human organ transplant operations were performed worldwide, including 90,306 kidney transplants (36% of living donors), 32,348 liver transplants (19% of living donors), 7,881 heart transplants, 6,084 lung transplants, and 2,243 pancreas transplants. However, this large number of transplantations barely covers 10% of global needs[2]. If these figures are extrapolated globally, the number of people in need of transplantation and those who die whilst waiting for the organ will continue to increase in the future.

These aspects predetermine the existence of a "black market" of human organs, the existence of criminal communities, including cross-border ones, involved in the illegal circulation of human organs and tissues. Demand creates supply, therefore, despite the almost universal ban on this circulation of human organs, the capacity of this black market on a global scale is billions of US dollars.

So, as an example, we can point to the Mastromarino case, considered in New York in 2008. Mastromarino was sentenced to 50 years for desecrating more than 1,800 corpses to be buried. This became possible due to the fact that he and his accomplices controlled several funeral homes. In fact, a criminal group organized a "supermarket" selling tissues and organs. Mastromarino even established Biomedical Tissue Services, which was a licensed company. In the course of the activities of this criminal group, more than ten thousand recipients received tissues and organs. These were taken without being tested for HIV, hepatitis, cancer, etc. As a result, a number of recipients were transfected with the corresponding diseases[3].

[1] "Australian Donation and Transplantation Activity Report 2017."
[2] "Global Observatory on Donation and Transplantation 2017."
[3] Goodwin, "Empires of the Flesh."

The book by Carla del Ponte on the participation of Kosovo Albanians in the killings of Serbs for the subsequent sale of human organs and tissues received even greater resonance. The leaders of the Kosovo Albanians, in particular Hashim Tachi, who was then the Prime Minister of Kosovo, were involved in this criminal story[4].

Perhaps the most apparent ethical argument against the commodification of human tissues and organs is that the creation of financial incentives for donation will undermine a central principle of bioethics — the free and informed consent of the donor. Financial incentives may even force impoverished people to give their organs to the more wealthy. The commercialisation of transplantology will lead to exploitation of poor people. As Goodwin argues, "selling organs will be tantamount to slavery, since weak, vulnerable social groups will turn into tool boxes, into boxes with usable spare parts devoid of humanity and individuality"[5]. However, as she has also explored, it may be necessary to work with the objective fact that there is a market for human tissues and organs. Goodwin concludes that one must stop turning a blind eye to the obvious, and in order to reduce the black market, it is necessary to allow the legalised commercialization of organ turnover in order to recognize their civil objectivity and donor's ability to remunerate their body posthumously[6].

The development of 3D bioprinting for cardiac regeneration is an attempt to develop a new medical therapy to address the deficiency of donor hearts. However, the rapid progress of 3D bioprinting threatens to outstrip its evidence base. Scientific and mainstream media hype may cloud the ability to reach reliable conclusions free from bias and exaggeration of results. The bold expectations of the research community are already reflected in some forecasts (Fig.1)[7]. It is notable that in the current year 2020, the forecast predicted the first implantable artificial heart and the image implies a close replica to the native human heart. There is a danger with infographics of this kind that they are not peer reviewed, not based on robust evidence and give the reader the impression of being more reliable than they are in reality. Perhaps future readers of this article in 2040 can attest to the accuracy of the projections at the time but this example highlights the problem that the true scientific messages required for the research community and the public to make decisions may become adulterated.

[4] "The Hunt: Me and the War Criminals."
[5] Goodwin, "The Body Market."
[6] Goodwin.
[7] "Artificial Organs Become a Reality."

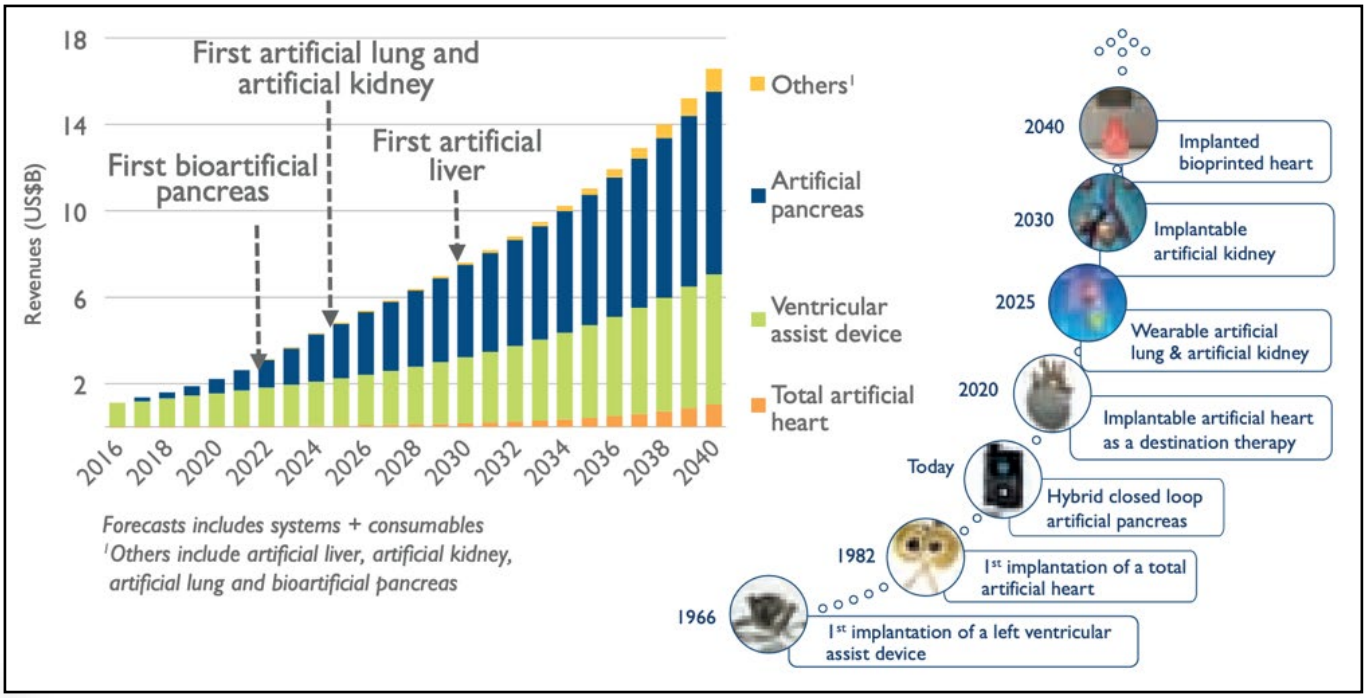


Fig. 1 Artificial organ market and roadmap from 2016 to 2040.

As well as the wrong message going out, the reception of the message may be influenced by social, cultural and religious phenomena.

Private companies exaggerating results and inflated dissemination by social media

Some commercial companies try to present their research using definitely bloated results. For example, the BIOLIFE4D company (USA) presented a patient-specific technology for treatment of the end-stage heart failure[8]. The company argues that a fully functioning heart will be created through 3D bioprinting using the patient's own cells. On the company's website there are many foggy information; furthermore, company declares "With BIOLIFE4D, a patient-specific, fully functioning heart will be created through 3D bioprinting and the patient's own cells, eliminating the challenges of organ rejection and long donor waiting lists that plague existing organ transplant methods"[9]. However, even last precise studies show that nowadays humanity does not have proper tools to create full and proper functional heart organ[10]. But with a closer look we can find that the company can provide only so-called "Mini-hearts" or "Cardiac Muscle Patches". The former ones lately show

[8] "Bioprinting Human Hearts, the BIOLIFE4D Process."
[9] "Bioprinting Human Hearts, the BIOLIFE4D Process."
[10] Varkey and Atala, "Organ Bioprinting."

promising results on swines[11]. Despite the loud statements on the main page of the site, BIOLIFE4D company's scientists in their publication adhere to rather modest opinion[12]. Moreover, the authors rightly emphasized that there are as technological as well regulatory challenges in this field, which attributed to the lack of large-scale commercial success in 3D bioprinting field[13].

Lack of actual and objective information about 3D bioprinting technology for the general public leads to situation when mass media inflates the findings of scientific papers. For example, in the Forbes Magazine the above mentioned BIOLIFE4D company is presented in a much better light. Forbes published news about this company with title "BIOLIFE4D Just 3D Printed A Human "Mini-Heart". Another vivid example of not quite truthful fact is published in a near-scientific mass media – Genetic Engineering & Biotechnology News Magazine. In April 2019, an article "First 3D Engineered Vascularized Human Heart Is Bioprinted" was published[14]. Authors of this paper refer to the report from Noor et al (2019)[15]. From the title of the article one can conclude that scientists created a ready heart for transplantation, which of course is not so. In the original report, Noor et al discuss the potential of their approach for engineering personalised tissue and organ replacement in the future. Such exaggerated reports overestimate expectations of a particular technology, and when general people find out that this was not entirely true this could negatively impact research funding.

Insufficient evidence and limitation of studies for reliable conclusion

Apart from exaggerated and inflated reports, there is another problem in proper development of 3D bioprinting technology, which relates to lack of robust evidence. First of all, it concerns the requirement to follow the guidelines and checklists for scientific publications. These simple steps can significantly enhance and improve scientific reports. Nowadays, there are two main guidelines in the animal research area: The ARRIVE Guideline and PREPARE Guideline[16][17]. Furthermore, scientists have at their disposal the "Gold Standard Publication Checklist" that allows them to verify the quality of the article before submitting it to an editor[18]. If we look at how many recent high-impact articles meet the criteria of these guidelines, we find that many papers do not follow the basic standards for

[11] Gao et al., "Large Cardiac-Muscle Patches Engineered from Human Induced-Pluripotent Stem-Cell–Derived Cardiac Cells Improve Recovery from Myocardial Infarction in Swine."
[12] Birla and Williams, "3D Bioprinting and Its Potential Impact on Cardiac Failure Treatment."
[13] Birla and Williams.
[14] "First 3D Engineered Vascularized Human Heart Is Bioprinted."
[15] Noor et al., "3D Printing of Personalized Thick and Perfusable Cardiac Patches and Hearts."
[16] Kilkenny et al., "Improving Bioscience Research Reporting."
[17] Smith et al., "PREPARE."
[18] Hooijmans, Leenaars, and Ritskes-Hoitinga, "A Gold Standard Publication Checklist to Improve the Quality of Animal Studies, to Fully Integrate the Three Rs, and to Make Systematic Reviews More Feasible."

good science. Some authors use an outdated guideline, do not indicate the year and reference for guideline, and some do not indicate that they followed any guideline at all (Table 1).

Table 1. Following ARRIVE / PREPARE guidelines and Gold Standard Publication Checklist

Authors	ARRIVE	PREPARE	Other guideline, year	GSPC*
Noor et al 2019[19]	-	-	-	-
Gao et al 2018[20]	-	-	GCULA[21], 1996	-
Noguchi et al, 2016[22]	-	-	GCULA, 1996	-
Wang et al, 2018[23]	-	-	-	-
Izadifar et al, 2017[24]	-	-	CCAC[25], 1989	-
Gao et al, 2017[26]	-	-	NIHGCULA[27], 1985	-
Gaetani et al[28], 2015	-	-	GCULA, 1996	-
Bejleri et al[29], 2018	-	-	-	-
Yeung et al[30], 2019	-	-	-	-
Maiullary et al[31], 2018	-	-	GDEP, 2010	-
Zhang et al[32], 2016	-	-	-	-
Mattapally et al[33], 2018	-	-	NIHGCULA, 1985	-

GSPC*- Gold Standard Publication Checklist, GCULA - Guidelines for the Care and Use of Laboratory Animals, CCAC- Canadian Council on Animal Care, NIHGCULA - National Institutes of Health Guide for the Care and Use of Laboratory Animals, GDEP - Guidelines from Directive 2010/63/EU of the European Parliament.

Continuing the topic of research limitations, we must highlight the additional problem of insufficient or lack of clearly visible results for qualitative reports. For instance, Noor et al (2019) argue that they produced fully vascularised and perfusable cardiac patches[34]. Undoubtedly, the authors did a great

[19] Noor et al., "3D Printing of Personalized Thick and Perfusable Cardiac Patches and Hearts."
[20] Gao et al., "Large Cardiac-Muscle Patches Engineered from Human Induced-Pluripotent Stem-Cell–Derived Cardiac Cells Improve Recovery from Myocardial Infarction in Swine."
[21] National Research Council (US) Institute for Laboratory Animal Research, *Guide for the Care and Use of Laboratory Animals*.
[22] Noguchi et al., "Development of a Three-Dimensional Pre-Vascularized Scaffold-Free Contractile Cardiac Patch for Treating Heart Disease."
[23] Wang et al., "3D Bioprinted Functional and Contractile Cardiac Tissue Constructs."
[24] Izadifar et al., "Bioprinting Pattern-Dependent Electrical/Mechanical Behavior of Cardiac Alginate Implants."
[25] "CCAC - Canadian Council on Animal Care: Fundamental Principles."
[26] Gao et al., "Myocardial Tissue Engineering With Cells Derived from Human Induced-Pluripotent Stem Cells and a Native-Like, High-Resolution, 3-Dimensionally Printed Scaffold."
[27] "NIH Guide for Grants and Contracts, Vol. 14, No. 8, 25 Jun 1985. Special Edition : Laboratory Animal Welfare. - NLM Catalog - NCBI."
[28] Gaetani et al., "Epicardial Application of Cardiac Progenitor Cells in a 3D-Printed Gelatin/Hyaluronic Acid Patch Preserves Cardiac Function after Myocardial Infarction."
[29] Bejleri et al., "Bioprinted Cardiac Patch Composed of Cardiac-Specific Extracellular Matrix and Progenitor Cells for Heart Repair."
[30] Yeung et al., "Cardiac Regeneration Using Human-Induced Pluripotent Stem Cell-Derived Biomaterial-Free 3D-Bioprinted Cardiac Patch in Vivo."
[31] Maiullari et al., "A Multi-Cellular 3D Bioprinting Approach for Vascularized Heart Tissue Engineering Based on HUVECs and IPSC-Derived Cardiomyocytes."
[32] Zhang et al., "Bioprinting 3D Microfibrous Scaffolds for Engineering Endothelialized Myocardium and Heart-on-a-Chip."
[33] Mattapally et al., "Spheroids of Cardiomyocytes Derived from Human-Induced Pluripotent Stem Cells Improve Recovery from Myocardial Injury in Mice."
[34] Noor et al., "3D Printing of Personalized Thick and Perfusable Cardiac Patches and Hearts."

job; however, in reality these patches are with just pipes inside, which 3D bioprinter printed according to its software, Fig 2.

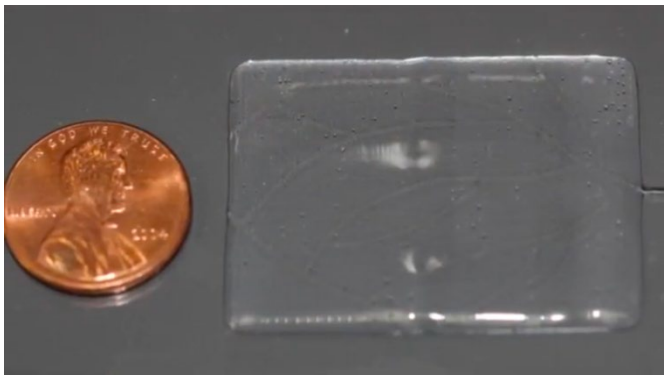


Fig 2. Fully vascularized and perfusable cardiac patches, according to Noor et al (2019).

Furthermore, authors did not provide the experiments on in vivo hearts but only implantation of the engineered patches between two layers of rat omentum. Which definitely cannot provide clear evidence of functioning of the vascularised patch and represents serious limitations to the study. In the concluding section of this paper, authors emphasise that long-term in vitro studies and in vivo implantation experiments in animal models should be conducted in order to adequately evaluate the fate and therapeutic value of the printed tissues.

Zhang et al (2016) argue that they created "vascularisation" in their tissue patches[35]. However, these structures are not perfusable and can demonstrate only “simulation results of flow velocity and oxygen distribution”. Furthermore, authors ignore the use of correct comparison tools. Many high impact studies in the 3D bioprinting field do not have the correct control groups.

As for animal experiments, scientists from this group did not show any *in vivo* experiments. Nevertheless, the authors state that such a technique could be translated to human cardiomyocytes derived from induced pluripotent stem cells to construct endothelialized human myocardium. However, this is not possible without extensive animal testing. Authors agree that further research should be done. It is expected that more advanced technologies are required to precisely print small diameter blood vessels within thick vascularised human heart constructs.

Ethical, social and religious perspectives

Any new technology needs to be accepted and supported by general society in order to reaching real success. The general public can influence on technology through socio-cultural and religious aspects. Under certain circumstances, some technologies that seem useful from the scientists’ point of view,

[35] Zhang et al., “Bioprinting 3D Microfibrous Scaffolds for Engineering Endothelialized Myocardium and Heart-on-a-Chip.”

still face difficulties in their development and dissemination. For instance, reproductive cloning is not accepted by the general public and therapeutic cell cloning is prohibited in France, Germany, Spain, Italy, Austria, Ireland, Israel, Sweden, Belgium, India, Canada and Australia but authorised in the UK, Denmark, Japan, the Netherlands and Korea[36] [37]. Furthermore, it is important to say that, despite their geographical proximity, the rules are very different. For instance, while it is authorised in Great Britain, it is prohibited in Ireland, authorised in Denmark but prohibited in Sweden[38].

Regarding the attitude of religion towards bioprinting research, we can say that it depends on many factors and types of religion. Different religions hold different views about a particular technology where human or animal cells are used. For example, the Catholic Church is completely opposed to research on human embryonic stem cells[39]. Because the Church opposes deliberately destroying innocent human life at any stage, for research or any other purpose, it has a deontological morale opposition to all embryonic stem cell research. However, when scientists proposed avenues for possibly obtaining embryonic stem cells or their pluripotent equivalent without creating or harming embryos…?then what happened?. Moreover, Catholic leaders were among the first to welcome this idea[40]. This attitude points to open opportunities for 3D bioprinting from Catholic point of view.

Islam, on the other hand, advocates research on embryonic stem cells as long as they benefit society with the least harm to embryos — the sources of stem cells[41]. One of the teachings of the Qur'an says: "And whoever saves one - it is as if he had saved mankind entirely" (5:32)[42]. Separately it is necessary to say about the attitude to the ultimate goal of these studies. In case of disease, Islamic religion points people to seek proper treatment and to take it when possible and refers to hadith "Seek medical treatment, for truly Allah did not send down a disease without sending down a cure for it"[43]. However, we should take into account that many Islamic patients cannot accept the use of porcine tissue[44]. Therefore, we can conclude with some reservations, that 3D bioprinting is permissible in that religion.

3D bioprinting adherents must take into account all aspects of human society; otherwise, the technology can meet insurmountable resistance. However, it is worth to say that any rejection of

[36] Henon, "Human Embryonic or Adult Stem Cells."
[37] Isasi and Knoppers, "Beyond the Permissibility of Embryonic and Stem Cell Research."
[38] Vijayavenkataraman, Lu, and Fuh, "3D Bioprinting – An Ethical, Legal and Social Aspects (ELSA) Framework."
[39] "Catholic Support for Ethically Acceptable Stem Cell Research."
[40] "Newark Archbishop among Supporters of Experimental Stem-Cell Technique."
[41] Al-Hayani, "Muslim Perspectives on Stem Cell Research and Cloning."
[42] "The Quranic Arabic Corpus - Translation."
[43] "If a Sick Person Refuses Treatment and Bears It with Patience, Will He Attain the Reward?"
[44] Enoch, Shaaban, and Dunn, "Informed Consent Should Be Obtained from Patients to Use Products (Skin Substitutes) and Dressings Containing Biological Material."

something new can drastically change with accumulation of personal experience, which includes, of course, the free acquisition of knowledge about capabilities of a particular technology. That is why any new technology must be explained in simple and understandable language so that it affects personal experience, motivation, emotions and leads to an objective intentional positive attitude of all sections of society without exception.

Fortunately, 3D bioprinting does not face fierce resistance in modern society as a whole. The social challenges around 3D bioprinting have received little commentary despite the schism between social promise and progress in technological terms[45]. However, as scientists working towards the success of bioprinting, we have to maintain a clear understanding of this technology for all people.
Taking into account that our society is developing and perspectives of people are dynamic and what may not be acceptable today may be accepted after a few years from now. Anyway, we want to believe that more and more people will understand the need for this kind of research.

Legislation and regulation in different countries

As mentioned above, our society as a whole is not opposed to bioengineering in terms of socio-cultural and religious aspects; however, existing legal standards, regulatory processes and diversities can potentially limit the development of bioprinting technology[46]. At the moment there are few regulations for bioprinting applied to research purposes[47]. However, bioprinted products used in clinical applications should satisfy The Food and Drug Administration (FDA) or The General Medical Council (GMC) regulatory oversight in the future. The bio-inks which are used in the process of bioprinting should be manufactured using a strict regulatory guideline. The implementation of Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) by FDA in the year 2011 aims to prevent the introduction or transmission of potential communicable diseases[48]. The Australian Code of Good Manufacturing Practice (cGMP) follows the same principles[49]. According to these documents there is an assumption that the 3D bioprinted tissues will not be regulated as human organs for transplantation but will be more likely to be regulated as a drug, device or biological products.
Furthermore, there are other critical criteria such as control of the quality and process validation procedures can also be applied along with good manufacturing practices, the bioprinted tissues still create difficulties in regulatory approval due to increasing complexity of clinical research. As of now,

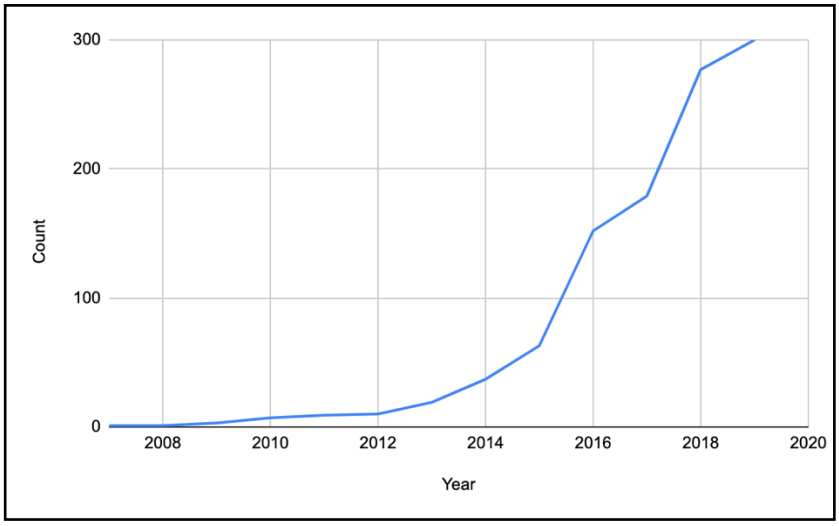
[45] Vermeulen et al., "3D Bioprint Me."
[46] Williams, "The Same but Different."
[47] "The Key Questions of the 3D Printed Organ Market | Biogelx."
[48] Research, "Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)."
[49] Wright et al., "Raising the Standard."

there are no manufacturing standards for bioprinting process and this current lack of regulatory actions needs to be rectified prior to the utilisation of 3D bioprinting on a clinically relevant scale[50].

Conclusion

Bioprinting of tissues is a result of multidisciplinary team work, which includes biologists, engineers, computer science specialists and medicine professionals. Undoubtedly, it requires a significant amount of financial and specialist resources. According to PubMed library, in the last 5 years the number of publications of articles related to 3D bioprinting increased at 10 times, Table. 2.

Table. 2. 3D bioprinting articles, results by year.



Scientists have demonstrated ground-breaking research in tissue fabrication. However, in this area there are still many challenges, related not to specific technological but also ethical and legal aspects. Considering a successful development, the pathway from 3D bioprinting of tissues or organs to implantation into a human contemporary society has to elaborate special protocols involving fabrication techniques, surgical and postsurgical care; furthermore, this pathway should avoid unnecessary hype and unobjective reports. It can be possible with development of highly repeatable and straightforward technologies to print the tissues and organs in logical steps, from simple to complex.

A great care should be taken to ensure that the financial resources for bioprinting studies are properly allocated, in the best interests of the potential patients and taxpayers. On the other hand, researchers

[50] Chua, Wong, and Yeong, *Standards, Quality Control, and Measurement Sciences in 3D Printing and Additive Manufacturing*.

and scientists should not provide false reports to attract more funds. A global registry for the pre-clinical, clinical and long-term follow-up trials in the bioprinting area will help in better transparency. Increased transparency, disclosure of information, and discussion of uncertainties regarding outcomes with clinical trial participants will also help to improve development of the technology.

A scientific-oriented regulation of the bioprinting process should be developed. 3D bioprinted products require a comprehensive regulation to assure quality control in every step of the process. In addition, for the successful development of bioprinting, the ethical aspects of the technology still need to be taken into account. Nowadays the vast majority of the researches have been made on laboratory animals. Before we truly learn how to bioprint human organs ready for implantation, our society must develop acceptable ethical standards for this technology. This is necessary so that when 3D bioprinting is translated to clinical practice developed we do not meet barriers to the wide clinical induction of technology in terms of ethical, legal or regulatory challenges.