

## Article

# 3D Bioprinting and Organ Transplantation: Patient Dream or Ethical Nightmare?

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**Abstract:** With the advent of recent advancements in biotechnology and digital manufacturing, organ manufacturing and transplantation have become a reality nowadays. This paper describes a detailed overview of the success and challenges of bioprinting and organ technologies, its realization in today's age, and ethical concerns that complicate its prevalence and popularity in society. The advances are promising and the research areas are numerous because the benefits are enormous for the patients. The technology has the potential to revolutionize the healthcare market and particularly the pharmaceutical sector by solving some key issues after going through a long and expensive process of research and development of such new treatments. The current study aims to foresee a promising development in the manufacturing of artificial organs and hopes that it will be accessible to people very soon after satisfying some major ethical concerns.

**Keywords:** bioprinting; tissue engineering; regenerative medicine; ethics in technology

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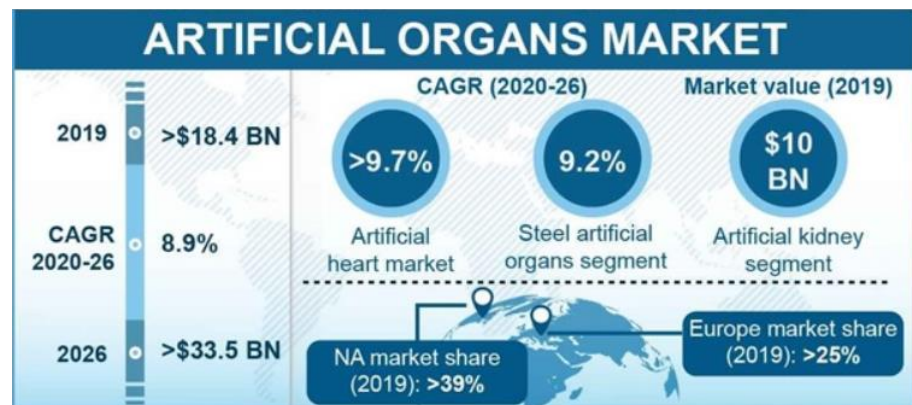


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## 1. Introduction

Tissue-engineered medical products (TEMPs) and 3D Bioprinting is a biomedical application of additive manufacturing processes for artificially producing biological tissues. Their purpose is to replace the damaged tissues and organs. The 3D Bioprinting process is the spatial structuring of biological cells by piling them together using a computerized method of layering. This is required in order to grow living tissues and organs for further use in biological research e.g. regenerative medicine, tissue engineering, and pharmacokinetics applications (Pountos, Tellisi, & Ashammakhi, 2019). 3D bioprinting can be regarded as the next horizon in biomedical and allied healthcare fields to treat patients suffering from ailments requiring organ transplant. In principle, the key use of imprinted organs is for transplantation (Gu, Fu, Lin, & He, 2020). Therefore, current research is aiming to develop artificial structures for the heart, liver, kidneys, and other vital organs of the human body. Nevertheless, challenges exist in developing the tiny parts of the heart like heart valves, which are also being realized. Some imprinted organs have now passed through clinical trials but the main technical concern includes the reconstruction of hollow structures e.g. vascular structures, which may require a zero gravity environment for development and maturity for possible implantation in the human body.

This paper is organized as follows: Section 2 describes a survey of existing potential of these technologies followed by an exhaustive overview of the technological issues and limitations in bioprinting and artificial organ transplant in Section 3. In Section 4, some key ethical concerns and societal challenges are discussed that must be addressed to promote this technology. Finally, Section 5 concludes the paper.

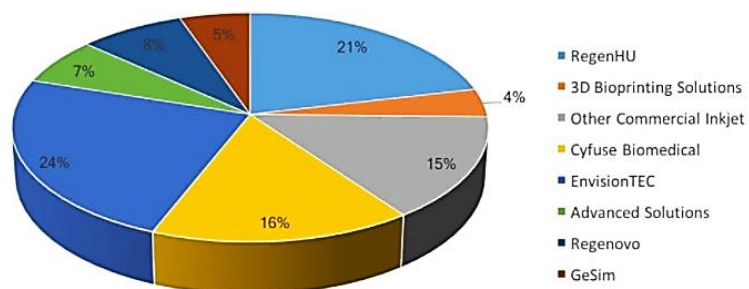


**Figure 1** Bioprinting and artificial organ market statistics (Sumant Ugalmugle & Swain, 2020)

## 2. Market Potential in Bioprinting and Organ transplantation

Today, many people are waiting to receive an organ for a transplant. The demand is high and the chances of obtaining it are all fairly low. In France only, nearly 24,000 patients were awaiting an organ in 2017 and only 6,000 people could get them transplanted. Bioprinting could eventually overcome this problem by being one of the developments in the 3D industry which has experienced the most significant growth in recent years, along with remarkable innovations (Dey & Ozbolat, 2020). A recent report published by GMI in 2020 estimated the bioprinting and artificial organ market at 33.5 billion dollars by 2026, against 18.4 billion dollars in 2015. Based on these forecasts, this market is anticipated to grow by a compound annual growth rate (CAGR) of 8.9% by 2022, far exceeding many markets related to 3D printing (Sumant Ugalmugle & Swain, 2020).

The expected key players are the United States and Canada, followed by Europe with England and Germany as leaders. This growth can be explained in particular by the appearance of more accessible and less expensive systems (i.e. printing systems at less than 20,000 dollars), thus facilitating the diffusion of bioprinting in the industry as well as in universities. This growth has accelerated by the entrance of large multinational companies in the market such as Roche, Astellas Pharma, Bristol-Meyers Squibb, Merck, and Novartis. Thus, the growing number of research programs conducted on bioprinting could lead to the creation of more than 5,000 bioprinting systems around the world by 2027 (Combella, Jessop, & Whitaker, 2018).



**Figure 2** Professional 3D bio-printer market share (Smarttech, 2021)

As we have seen, bioprinting is a technology, which is developing extremely rapidly but which also facing complex technical limits to grow further. Today, bioprinting robotic technologies are mainly concerned with the production of organic tissues that are simple to print compared to the printing of organs such as a kidney, a liver, or even a heart, which have extremely complex structures. Indeed, it is necessary to solve the problem of printing complex vascular structures to design a large organ, which must ensure nutritional

exchanges at the scale of all the tissues in order to sustain and work for the predicted life. Some key players in the bioprinting market are shown in Fig. 2.

Table 1 briefly lists some famous entrepreneurs in bioprinting and their technology type for tissue regeneration.

**Table 1** Popular companies in bioprinting technology

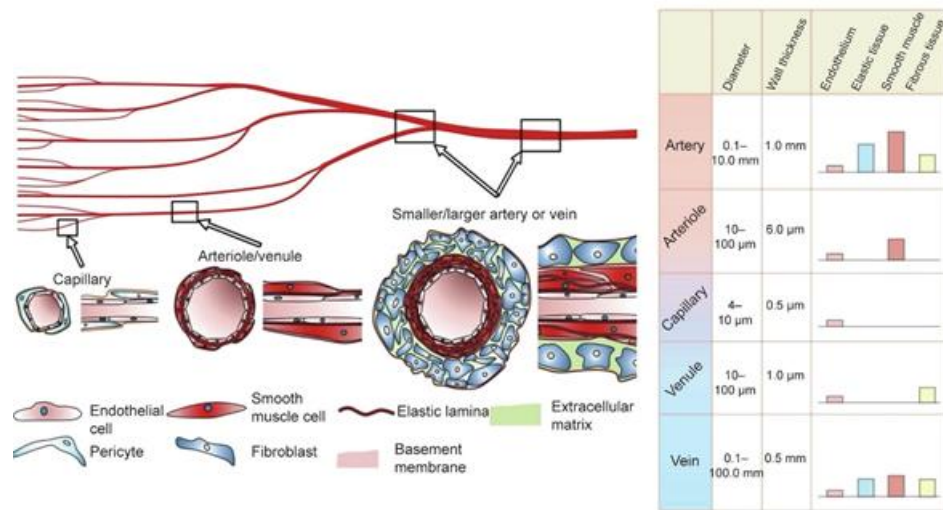
Sr. No	Developer	Location	Bioprinter	Technology	Application
1	ASPECT	Canada	RX1™	Lab-on-a-Printer (LOP™)	Tissues
2	ALLEVI	USA	Allevi 6 (Biobot 2)	Extrusion-based	Tissues
3	CELLINK	Sweden	BIO X	Droplet/Inkjet/Extrusion	Tissues (Cartilage/Skin)
4	CYFUSE	Japan	Regenova	Kenzan Method	Tissues
5	DIGILAB	USA	CellJet Cell Printer	synQUAD	Cells
6	RegenHU	Switzerland	3DDiscovery™ BioSafety	Droplet/Inkjet/Extrusion	Bone Tissue and Skin Tissue
7	3D Bioprinting Solutions	Russia	FABION	Extrusion-based	Tissues (Cartilage)
8	Envision TEC	USA	3D-Bioplotter	Photo-Curing/Inkjet	Tissues
9	Advanced Solutions	USA	BioAssemblyBot (BAB)	Scan-Design-Print	Tissues
10	Regenovo	China	Bio-architect X	3D reconstruction of micro-computed tomography (MCT)	Tissues
11	GeSim	Germany	μCP6.1	Pneumatic stamping	Cells

### 3. Technological Challenges of 3D bioprinting

3D bioprinting is the development of cellular structures by means of 3D printing methods. Generally, 3D bioprinting uses the layer-by-layer printing method to pile up ingredients referred to “bioinks” for creating natural biological tissues, which are then utilized in the fields of biomedical engineering (Ahadian & Khademhosseini, 2018). Bioprinting uses a wide variety of materials compatible with the human body. At present, bioprinting is used for printing tissues and organs, particularly for pharmaceutical research. The first patent witnessing the feasibility of this technology was filed in the United States in 2003 and granted in 2006 (Iram, a Riaz, & Iqbal, 2019).

In order to clearly understand the challenges in bioprinting of blood vessels, it is important to first understand the histology of the human tissues. The inner diameter (ID) of the blood vessels ranges from less than 1mm to greater than 6mm (Cao, Maharjan, Ashfaq, Shin, & Zhang, 2021). However, capillaries (ID < 10 µm) are extremely thin and are formed from a single layer of endothelial cells which form the inner lining of the blood vessel as shown in Fig. 3. Various bio-printing techniques are being investigated in recent years to reproduce these vessels using vascular tissue engineering. However, simultaneous satisfaction of biocompatibility standards, taking into account the requirements of mechanical properties to withstand the blood pressure and compliance similar to the native vessel and acceptable suture retention are some important aspects to take into account (Arif, Khalid, Ahmed, & Arshad, 2022). Thus, there is a stringent requirement on the physical, biological, chemical and, mechanical design for the processability of these vessels. As it is

required that the design remain within the feasibility window offering low manufacturing costs, serializable structure, and easy storage which pose additional limitations.



**Figure 3** Schematics of different types of blood vessels with cell composition, diameter, and thickness. The bar represents the relative proportion of various layers of blood vessel (Cao et al., 2021).

Thus, the design of bioinks, which can be utilized for the required bioprinting resolution offering sufficient integrity of that vessel, is the root cause of this delay in realizing these vessels. Some bioinks are low cost in manufacturing but they are not structurally viable; some others are mechanically strong but lack biocompatibility, poor cell adhesion, drop in mechanical strength due to the degradation process and release of toxic byproducts (Fazal, Raghav, Callanan, Koutsos, & Radacsi, 2021). Thus, improved bioprinting processes are required to be devised along with the progress of advanced bioinks for producing functional small-diameter vascular grafts and tissues with required biological and mechanical performance.

As perceived from the above discussion, bioprinting is a multidisciplinary technology visualizable via interconnection of medicine with material science and engineering. We can distinguish several stages of tissue engineering by 3D bioprinting. These three sequential technological steps are pre-processing, processing (printing) and post-processing. Among the technical challenges faced by the scientists, following are the key bottleneck areas:

### 3.1. Complex vascularization

Currently, scientists are unable to reconstruct blood vessels e.g. capillaries as they are extended, thin, and tubular in structure to be built by present day printers with limited accuracy (Tomasina, Bodet, Mota, Moroni, & Camarero-Espinosa, 2019). The realization of a functional organ is hence impossible as it is challenging to supply oxygen and glucose at the cellular level and therefore they would die very quickly. Thus, the skin cell tissues printed so far are not vascularized and therefore are not transplanted yet.

Moreover, due to the greater complexity of the nervous system, bioinspired materials are required (Qiu et al., 2020). In the absence of nerves, the muscles created cannot be actuated and therefore cannot be transplanted (Datta, Ayan, & Ozbolat, 2017).

### 3.2. Limited lifetime of the printed cells

Until today, printed tissue fabric do not have stay long as they are in artificial environment (Moldovan, 2019). For example, the miniature kidney bio-printed by the “Organovo” remained “alive” for only 5 days which is still considered a remarkable effort.

### 3.3. Price Issue

3D-printed organs are very expensive. Small research laboratories or hospitals can therefore hardly acquire them. Indeed, a biological printer costs several hundred thousand euros, a cost that can only be bear by larger research facilities. Biomimetic approaches are underway to produce cheap bioprinters (Tong et al., 2021).

### 3.4. Complex organization of organs

As in the case of the kidney, it is composed of a million units (or nephrons) that filter the blood and produce urine. Each nephron is further made up of multiple subunits like the glomeruli, which are further composed of four different types of cells (Humphreys, 2021). This configuration is therefore very complex for layer-by-layer printing.

### 3.5. Gravity

Scientists are required to print tissues layer by layer due to the problem of gravity, even by using a modern printing technique. This actually complicates the development of large organs that would collapse due to their own weight and distort the molecular structure of the organ. A microgravity environment has been proposed for bioprinting in space to avoid collapsing of the microstructure as experimented on earth (Lu & Groh, 2022).

### 3.6. Scientific knowledge

This is surely the main hindrance in the realization of complex organs. After having a grasp on sophisticated technologies, we still lack appropriate knowledge about the complex human body. This is especially true for the case of the Brain and associated nervous system which requires complex methods for bioprinting (Esworthy et al., 2019).

## 4. Ethical Issues and Societal Challenges in 3D organ printing

Because of the immense hopes it arouses, bioprinting is a technology that will lead to many ethical disputes and raise a number of moral and sociological questions (Gilbert, O'Connell, Mladenovska, & Dodds, 2018). The four key ethical principles, that is beneficence, non-maleficence, autonomy, and justice must not be compromised while implementing this technology (Beauchamp, Beauchamp, & Childress, 1994). Whereas, the societal challenge refers to health inequities that challenge all countries around the globe. In general, they are interrelated and hard to separate explicitly. Following are some key ethical issues:

### 4.1. Usage of Stem Cells of Embryonic Origin

As bioprinting is based on the usage of stem cells, which can be multiplied further and specialized. Subject to the type of these cells (embryonic origin), ethical concerns will therefore necessarily arise. Indeed the differentiation between the embryonic and adult stem cells is essential. The primary characteristic of embryonic stem cells is that they are pluripotent, meaning that they can develop into any type of body cell.

However, research with human embryonic stem cells (hESCs) requires the destruction of embryos and involves medical risks of oocyte retrieval among other ethical issues (Lo & Parham, 2009). On the other hand, human adult stem cells (hASCs), are multipotent, i.e. they can only grow into certain types of tissue. For example, adult bone marrow stem cells are capable of differentiating into skeletal muscle, brain microglia and astroglia, and hepatocytes (Moghaddam et al., 2021). In addition, the hESCs are immortal, meaning they can divide indefinitely, can be freely grown in culture, and show distinctive properties, which include spontaneous differentiation into three germ layers in vitro or

teratoma formation in vivo. Whereas hASCs are rare, undifferentiated cells present in numerous adult tissues.

Currently, the use of embryonic stem cells for tissue engineering purposes is already generating intense debate on the international scene and there are marked differences in perceptions between different countries (Lo & Parham, 2009; Moghaddam et al., 2021; Zhang, Peng, & Zou, 2018). These strong differences in views could intensely impact the way in which bioprinting could be (or not) accepted, or in any case slow down its development and uses (Vermeulen, Haddow, Seymour, Faulkner-Jones, & Shu, 2017).

#### *4.2. Expensive Technology*

Since, bioprinting is a recent and advanced technology that is potentially expensive; it could only be available to the rich populations who can afford them. This seems to be a serious societal challenge referring to unequal opportunities for all, since this could lead to a division of populations based on their income and allow the richest people to live longer and healthier lives. The question of equal access to healthcare, and to this technology in particular, among populations, will therefore inevitably arise (Pountos et al., 2019). It is a requirement that 3D bioprinting should not exacerbate current geographical and socio-economic discriminations but seek to mitigate them by offering low-cost options to people belonging to developing economies.

#### *4.3. Artificial Evolution of Human*

The scientific problem of cloning includes three major types i.e. Gene cloning, therapeutic and reproductive cloning. Human cloning has two major types, i.e., reproductive and therapeutic cloning. Reproductive cloning aims to duplicate a human to his/her offspring who resembles his/her parent exactly. Whereas, Therapeutic cloning is used to produce stem cells from the embryonic clone. Therapeutic cloning produces cloning cells from a human for onward use in medicine and transplants. Although, it is an active research area, but is not in practice anywhere in the world, as of 2022 (Pal, 2022).

Gene cloning yields copies of genes or DNA segments while, reproductive cloning generates copies of whole animals. Embryonic stem cells are produced by therapeutic cloning which is further utilized for producing tissues in order to replace injured or ailing tissues. Gene cloning or DNA cloning is different from reproductive and therapeutic cloning as the later techniques share many of the same techniques but are done for different purposes (Zhang et al., 2018). Cloning new organs from stem cells can benefit people waiting for donor organs for years. Cloning can be considered as reprogramming a cell by substituting its nucleus with another cell's nucleus so it develops into the genetic equivalent of the original cell.

In the longer term, the improvement in human capacities and performance by bio-imprinted organs and the resulting prolonged life expectancy could pose serious bioethical problems when faced with what some scientists call the "artificial evolution" of man (Gilbert et al., 2018; Kirillova, Bushev, Abubakirov, & Sukikh, 2020; Vermeulen et al., 2017). If we look even further, it is questionable whether the future of bioprinting could be the full cloning of human organisms. There are serious ethical concerns and societal challenges in determining the effects of reproductive cloning on the child/parent relationship which also includes appropriate legislation and regulation (Dukanovic, 2021). Whether or not a clone would ever be able to develop into a self-sufficient entity is also key to determine yet. Currently, bioprinting seeks to replace failing bones, organs, and tissues, but it is not unthinkable that this technology (combined with other advanced technologies) allows the bioprinting of a human from the synthesis in the extremely distant future (Kirillova et al., 2020).

#### *4.4. Technology Challenges in replicating Complex organs*

Apart from the obvious contravention of any current ethical code, a point that seems to be in agreement among researchers is that the organic reproduction of the brain, the most complex of the human body, is extremely difficult if not impossible (Oliveira et al., 2019; Sanjairaj Vijayavenkataraman, Yan, Lu, Wang, & Fuh, 2018). Some recent 3D and 4D combinational techniques however studied the effects of cortical folding on stem cell proliferation and maturation (Esworthy et al., 2019). Some major ethical concerns related to replicating the brain are inevitable while considering the apprehensions related to memory and intelligence, which can be altered through a bio-printed brain (Qiu et al., 2020). Moreover, bioprinting may empower plastic surgeons to print body parts or tissues that are more aesthetically pleasing to substitute undesirable parts which can be easily misused to enhance human capability (Varkey & Atala, 2015).

#### *4.5. Cost-benefit analysis of the Technology*

The printing of organs from the recipient's cells could eliminate the risk of rejection, thereby saving several lives, lowering the costs of medical care, and meeting the necessary organ demand for disabled in the society (Matthews, Pandolfo, Moses, & Gentile, 2022). To date, the creation of the complex vascularity necessary for oxygenation and organ nourishment remains a barrier. Indeed, making a solid mass of flesh is "relatively" easy, but adding a means to pump blood and other nutrients through the flesh is much more difficult (Cui, Nowicki, Fisher, & Zhang, 2017). Thus, if the bioprinting of organs for transplant use proves to be an exciting horizon for researchers, the major technical problems encountered arise at the level of the cost payable to implement the complexity of the functions of these organs and the large number of blood vessels that nourish them (Sanjayraj Vijayavenkataraman, Lu, & Fuh, 2016). Therefore, only a rigorous cost-benefit analysis per patient can confirm its impact on human society and health economics.

#### *4.6. Highlighting Potential Risks*

While appreciating the significance of this emerging technology, it is imperative to acknowledge the ethical problem of having 3D bioprinting enthusiastically depicted in mass media, which in reality is a hyped narrative, which ignores targeting risks, associated with the technology. An expert study shows the overly positive bias of media portraying 3D bioprinting showing that only a little care has been given to potential safety issues or other associated risks of 3D bioprinting (Gilbert, F., Viaña JMN, O'Connell, C., Dodds S., 2018). Therefore, it is indispensable to discuss risks and problems, instead of mostly focusing on positive aspects of this technology in the media.

#### *4.7. Regulatory Issues*

There are currently considerable regulatory uncertainties concerning 3D bioprinting in the healthcare community. For example, in the United States, the Federal Drug Administration (FDA) does not address the integration of biological, cellular, or tissue-based products in 3D printing. The current guidelines issued by FDA mention the Center for Biologics Evaluation and Research (CBER) for assessment of the 3D printing and related products containing biologics, cells or tissues. However, CBER has not yet developed clear guidelines to explicitly address 3D bioprinting and associated technologies (Gilbert, F., Viaña JMN, O'Connell, C., Dodds S., 2018).

### **5. Conclusions**

Despite the gigantic challenges, progress is being made in skin grafting, and scientists are now able to produce fully functional human skin from different skin stem cells of the same person. Progress is slow and bioprinting is still far from being able to be optimally used, but there is no doubt that by observing the scientific and technological advances of our time, workable solutions will be implemented soon. Therefore, it is almost

certain that bioprinting will first test drugs and products intended for human use more effectively, and then develop personalized treatment solutions within a few years. In about ten years (~ 2030), researchers hope to be able to make functional tissues for regenerative medicine. Moreover, in 30 years or so, it is believed that this technological breakthrough would get mature enough for viable whole organ production and transplantation to be possible. Addressing the ethical issues combined with social and legal justice is a bit subjective and varies from one society to another. However, fundamental concerns need to be addressed by inviting social scientists and technology leaders together to find answers to the key ethical questions to make sure that bioprinting would not contribute to unfair therapeutic outcomes.

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