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# Alternatives to Organ Replacement

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**Abstract**

Organ replacement is the process in which an organ is replaced, this is done with the purpose of improving quality of life and helping patients suffering from damaged or malfunctioning organs, especially vital organs such as the heart, kidney, lungs, and many more that may affect a patient's health tremendously if not replaced. One of the most common and well known methods of organ transplantation is organ donation, in which an organ is removed from one body, to be placed in the patient's that is in need of a new organ whether it be from organ malfunction or the absence of an organ. But this method comes with multiple drawbacks, such as the patient's compatibility with the donated organ, ethical and religious issues, and organ shortage that can lead to in an increase of organ trafficking, which is when organs are removed illegally and without consent to be sold in the black market as a result of high demand for organs for transplantation and other medical usage. But with today's technology, multiple alternatives to organ donation and transplantation have emerged that provide solutions to the mentioned issues. Such as xenotransplantation, a process which involves the transplantation from one species of another, 3d bioprinting, 3d printing used to fabricate biomedical parts that imitate natural tissue, mechanical support, which involves using machines to provide support to failing organs, and other emerging technologies in development such as regenerative medicine, which can help regrow and replace tissues and organs, cloning from stem cells, and artificial organs. Although neither of these methods alone can solve the ongoing crisis as they are not ready, each method presents its own advantages and disadvantages, and should be improved and researched upon in order to find a solution closest to perfect for organ replacement.

***Keywords:*** Mechanical support; organ transplantation; regenerative medication; three-dimensional bioprinting; xenotransplantation.

## 1. Introduction

Death and disability are most commonly caused by disease and infection of the heart, liver, lungs, kidneys, and pancreas. But the majority have potential to be treated via organ replacement [1-4].

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The number of organ malfunction and failure alongside its effects will likely continue to rise, alongside the needs of patients for safer transplants [5]. Nowadays, technology is constantly being developed in various fields including organ transplantation in order to tackle the issue of limited availability of organs [6]. Some of these include the development of stem cells for transplantation, tissue engineering, xenotransplantation, cloning, and many more. Some of the mentioned developments claimed to have promising and ready solutions in the near future by researchers [7]. As exciting as it is, as of right now none of these are likely to be able to address and solve the need of organ replacements alone as they are still in development and in need of further research [8, 9]. There is currently a severe shortage of organs for transplantation that is likely to continue growing and worsen as time passes, this affects the rate at which optimum therapy can be delivered [10, 11]. Therefore, considering the issue at hand and how it can be solved is the appropriate measure to take [6, 12]. This literature review paper has the goal of exploring the aforementioned new technologies, the challenges that come with each of them, and vitality of organs that may solve this issue in the future.

## 2. Clinical transplantation

Donation of organs for transplantation and replacement currently remains the most cost effective and best solution for severe organ failure [1]. As of 2017, the most frequently replaced and transplanted organs were the kidney and liver in contrast to small bowel transplants which were the least frequent [13]. There are two significant types of donor and recipient relationship in organ donation and transplantation: specified, which refers to an intended or known donor who has some form of relationship whether by genetically or emotionally, such as a spouse donating their kidney to their husband would be considered a specified direct donation [14]. And a donation through an exchange program to a known recipient would be considered a specified direct donation [15, 16]. Unspecified donation refers to an anonymous recipient on a fixed waiting list. This can result in contraindications such as policies and infections, and long waiting lists that can be as long as 3-5 years, can become challenges to both donors and recipients [17, 18]. A big threat that comes with the process of transplanting organs is the shortage of organs, having been confirmed by statistics. Claiming that in 2015, 74.63% candidates in the US failed to obtain a transplant [1, 19].

A promising solution to this issue is Living Organ Donation or LOD [1, 20]. This procedure has already been established in some countries but is still ongoing in some [13]. In the US and Europe, the most common transplants done via LOD are the liver and kidney, which includes pre-emptive and early transplants [13, 20, 21]. Transplants can be given to those who suffer from kidney diseases even before their dialysis therapy in the case of pre-emptive transplants and can be given to those who suffer from kidney failure shortly after it happens in the case of early transplants [22]. Pre-emptive and early transplants can result in many benefits including a less chance of transplant rejection, avoidance of dialysis therapy, and improved quality of life [23, 24]. But LOD also comes with its issues, such as physical, psychological, and social risks alongside donor and recipient relationships and screening in varying countries [1]. This creates an unclear environment in regards to the protection of recipients and the graft donors [17]. Nevertheless, in order to achieve an improvement in safety and less troubled procedure of applications worldwide, information on acceptable practices regarding LOD is provided by the World Health Organization [17, 23]. A main source of organ transplants is through donation post brain death also known as DBD [25]. The essential criteria to determine brain death includes coma that is

irreversible and whose cause is known, brain stem apnoea, along with areflexia [25]. Afterwards, preparation for the procedures succeeding brain death includes a prognosis, haematologic testing, and examining the deceased body's pathophysiology's general changes in order to decide the practicality of a possible donation [25]. The argument over DBD's ethics has generated general philosophy, medicolegal, and religious debates with the connection and equality of brain death and death being one of the main controversies, with arguments using misconceptions regarding the possibility of the heart beating and body movements following brain death [21, 26].

## 3. Alternatives to organ transplantation

### *3.1 Xenotransplantation*

Xenotransplantation refers to the process involving the transfer of living cells, tissues, or organs between species, for example, from chimp to man [10]. Xenografts or xenotransplants are used to describe these cells, tissues, or organs. By contrast, allotransplantation refers to the transplantation of the same species. While xenotransplantation may offer a treatment option for terminal organ failures, along with raising several concerns ethically, legality and medically [11]. Porcine endogenous retroviruses or PERVS, are a particular concern to take into consideration as they are vertically transmitted microbes that are lodged in the genomes of swine [27]. Retroviruses refers to the remnants of old viral infections that have been discovered in the genomes of the majority of mammalian species [28, 29]. They are vertically transmitted through inheritance because they are integrated into the chromosomal DNA [29, 30]. Additionally, two PERV genomes that are defective have the ability to combine and form an infectious virus via complementation and genetic recombination [28, 30]. There are three subgroups of infectious PERVs, two of which have been shown to be able to infect human cells which are in culture [31, 32]. They accumulate over time due to the numerous deletions and mutations, although when in the host species, they are not infectious [32]. But, they have potential to become infectious when inside a different species [32]. All human-to-animal transplants were paused for this reason by multiple health organizations in 2005 [10, 19]. But in 2009, following a review by NHMRC which concluded with " the risks if appropriately regulated, are minimal and acceptable in light of the potential benefits," citing European Medicines Agency developments and World Health Organization in the management and regulation of xenotransplantation, it was repealed [33, 34]. Retrovirus testing is required for xenotransplant recipients by the FDA [33]. Along with potential risk of infections from animal to human, transplant recipients may risk infection to not only themselves but also to their family and society [29, 35].

Xenotransplantation is not ideal, even though the valves of pig hearts have been used without clear adverse effects for many years [34]. Nevertheless, they are essentially inert tissue that rarely elicits rejection [30]. Cells and tissues from pigs have also been used in the treatment of degenerative diseases such as Huntington's chorea or Parkinson's disease, and diabetes [2]. Another instance of xenotransplantation is the attempted transplantation of islet tissue from fish to nonhuman primates [11, 36]. The latter research endeavored for the purpose of paving the way for possible application for humans. An exciting review on cellular xenotransplantation was recommended, it sums up the current knowledge of xeno(allo)-cell transplantation's functional and immunological aspects [37]. Transplantations for cardiomyopathy, liver failure, diabetes, neurodegenerative

diseases, or bone regeneration [37-41]. Ovarian tissue xenotransplantation for naked mice which are immunodeficient have been previously used in the study regarding ovarian follicles' development [42]. Even when cryopreserved ovarian tissue was used, mature follicles managed to develop [43]. Both the graft and host vessels contribute to human ovarian tissue revascularization in mice that have been xenografted [44]. Similarly, xenografted tissue of fetal testis from humans exhibit typical function, structure, and development that includes differentiation of normal germ cells. This establishes an in vivo model for studying the human fetal testis's normal development and the possibility of factors originating externally causing disruption [45]. This ought to clarify the mechanistic basis for the fetal origins of testicular dysgenesis syndrome Or TDS disorders, and sexual development disorders or DSDs [41, 46]. Xenografts of human fetal testis provide an equivalent ex vivo model of the formation of normal seminiferous cord, development of germ cells, and production of testosterone [47]. No xenotransplantation trial has been entirely successful to date due to the numerous obstacles posed by the immune system of the patient [10]. This response is usually more severe than that seen in allotransplantation, possibly eventually resulting in xenograft rejection and even the recipient's immediate death [10, 48]. Organ xenografts can be susceptible to various types of rejection [48, 49]. There are two types of acute rejection: hyperacute rejection, a type of rejection that happens rapidly and violently [50-52]. Caused when xenoreactive natural antibodies bind to the donor endothelium, activating the human complement system, resulting in endothelial damage, inflammation, thrombosis, and necrosis of the transplant [52, 53]. And Acute vascular rejection, the interaction between the host antibodies, macrophages, and platelets and the graft endothelial cells [48, 54]. An inflammatory infiltrate composed primarily of macrophages and natural killer cells with a few T cells characterizes the response [48, 55]. The binding of XNAs causes the release of procoagulant factors such as cytokines and chemokines to the XNA receptors on leukocytes (VCAM-1) and leukocyte adhesion molecules such as ICAM-1 and E-selectin [30, 56].

### *3.2 Stem Cell Transplantation*

The current holy grail of modern biology seems to be stem cells as with the proper stimulation, these root cells can be generated into any body cell [57]. Currently, the best place to source stem cells from are human embryos [58]. Typically, these can be acquired from fertility clinics [59]. Additionally, significant research is being conducted in order to clone stem cells that originate from non-embryonic tissue [59]. Possibility of successfully obtaining stem cells out of nonviable, blastocysts produced asexually may resolve a portion of the current ethical issues over the concept of therapeutic stem cell research [7, 22]. An issue concerning current embryonic stem cell technology in humans is the issue regarding histocompatibility, because cells derived from fetal sources or *in vitro* fertilized embryos are practically allogeneic cells, or cells from another individual [7, 60, 61]. Meaning that if any cells derived from another individual are transplanted into another human being, they risk being rejected [57, 62]. Currently industries in the biotechnology field are attempting to create embryonic cells that are identical to those found in an adult human or autologous embryonic cell to address the issues [63]. Eventually, one of the following methods below may be required, additionally, recent researches indicate that parthenogenesis may be both feasible and also less contentious ethically [64, 65].

Hematopoietic stem cells or HSCs can be used for transplantation therapy, for restoring the hematopoietic or any other systems [62, 66]. That may be failing. In the case that traditional sources of HSC become unavailable,

the human cord blood or hCB transplantation has been shown to be an effective alternative treatment option. Investigations have proven that HSCs increased by dimethyl–prostaglandin E2 (dmPGE2) in vertebrate models [67, 68]. Studies in utilizing HSCs from both human and nonhuman primates, indicated the therapeutic value of dmPGE2 [66, 69]. After xenotransplantation, it has been demonstrated that demethylated PGE2 vastly increased total human hematopoietic colony formation in vitro and engraftment of unfractionated and CD34(+) hCB, making it suitable for an FDA-approved clinical trial in phase1 [61, 70, 71].

*Ex vivo* treatments by living cells, for instance the routine blood stem cells from the umbilical cord preservation, can be expected to become more common in the future, with human tissues competing with animal sources for these treatments momentarily [7, 66, 71]. Additionally, as demonstrated with Dolly the sheep, cloning from mature cells may enable the regeneration of human tissues that are functional and, eventually, somatic cells organs [15, 72, 73]. The reprogramming of cell differentiation may soon allow patients to become donors for their autografts, negating the need for xenografts in diseases that are otherwise terminal due to irreversible damage to vital organs and tissues [66, 74].

### *3.3 Clone Technology with the purpose of creating Specific Cells*

Human cloning is creating an identical copy of an individual, a cell, or a tissue genetically [75, 76]. This term usually refers to artificial human cloning, although it is common for the cloning process to occur naturally such as human clones in identical twins [76]. However, genes influence behavior and cognition [73]. The most frequently used method for human cloning is somatic cell nuclear transfer. In this procedure, an egg cell obtained from a donor is enucleated and is then fused with another cell containing the identical genetic material in order to create a clone [75, 76]. Parthenogenesis is another technique that is only effective on females. This method requires coaxing an egg that is unfertilized to divide and cultivate in the manner of a fertilized egg [73, 75, 76]. Cloning has several disadvantages, including uncertainty, the probability of inheriting a disease or the possibility of an autoimmune response being initiated in the cloned product of life, alongside the potential for it to be abused [73]. Clones are likely the ideal organ donors [76]. Consider a bright young man suddenly diagnosed with lung cancer and requires a transplant [76]. Following surgery, the new and foreign organ is rejected by his body [73]. Cloning may be the answer to this issue [76]. The ideal solution to ensuring the human race's continued health and the happiness of many [73].

### *3.4 Organ Culture in Three Dimensions*

Biofabrication, an engineering approach that is the process of utilizing raw materials including molecules, living cells, biomaterials, and extracellular matrices to create complex biological products [77, 78]. To translate the concept of embryonic tissue fluidity into a developmental concept in biology allows the assembly of specific tissues and organs [79]. This technology regarding tissue engineering holds the promise of resolving the crisis of organ transplantation. However, assembling soft organs that are vascularized and three-dimensional is significantly hard and challenging [65]. Computer assisted organ printing and the engineering of 3D tissues of living human organs may provide hope. The printing of organs requires either "blueprints"of the organs or the actual printing of an organ, the conditioning, and the acceleration of its maturation [80]. This could be

accomplished through the use of a cell printer which prints layer-by-layer of gels that are placed sequentially and a solidified thermoreversible gel's sheer layers, which are used like paper for printing [81, 82].

### *3.5 Artificial Organs*

Artificial organs as a transplant substitute refers to artificial devices that are integrated or implanted into the body of a human with the purpose of replacing a natural organ to restore function whether it be a group of related functions or a specific function, allowing patients to promptly continue their everyday life [83]. Each system can be aided by practical devices such as the following [84]. Pacemakers for the Brain are devices that can transmit electrical impulses up to the brain, they can be used for uncontrollable epilepsy treatment [9, 83, 85]. Cardia and Pylorus valves, a gastrointestinal canal's closure systems are classified into three types: constrictive sphincter, dilatory closure, and kinking closure [38, 86]. Corpora Cavernosa, both of them can be replaced surgically and irreversibly via manually inflatable penile implants to treat erectile dysfunction in men who have failed to respond to all other treatment options [9]. Cochlear implants, thin-film array electrodes were placed successfully into a human's cochlea with minimal damage through the usage of an insertion test device (ITD), they are well-liked by the majority of recipients [9]. Artificial eyes, a function-replacing artificial eye that is most successful to date comes in the form of an implantation of a small digital camera possessing an remote unidirectional electronic interface onto the optic nerve, retina, and other relevant locations within the brain [87]. Artificial hearts are reserved for patients awaiting transplantation who are nearing death , having the capability to prolong life for up to 18 months [88]. Artificial pacemakers are electronic devices that have the ability to intermittently augment the natural living cardiac pacemaker (defibrillator mode), continuously augment, or bypass it entirely as needed. They have been so successful that their success has made them become widely used [89]. Ventricular assist devices, mechanical circulatory devices that can be used to wholly or partially replace a failing heart's function without removing the heart [3, 90].

Artificial limbs, some possessing semi-functional hands, some possessing opposable "thumbs" with the addition of two "fingers," or legs that have feet that can absorb shock that have the capability to allow a patient to run with training, being some options for patients [91]. Artificial Livers, hepatocytes, liver dialysis, and liver dialysis devices [92]. A stem cell-based bioartificial liver device to treat liver failure is being developed by HepaLife [93]. It is only possible because genuine liver cells (hepatocytes) are used, although this substitute for the liver is not permanent [9, 93]. Artificial lungs, appearing to be a near success [12, 94]. MC3, a company based in Ann Arbor, is currently developing this device. Indeed, an artificial lung refers to a technical device used to provide life support which can be used when the lungs fail to provide adequate oxygenation [90]. And from a long-term development standpoint, artificial lungs ought to be implanted permanently to replace the human pulmonary function whether it be partially or entirely [4]. Artificial pancreas, containing the ability to treat diabetes with several techniques that seem promising which integrate living tissue that are donated encased in unique materials that can avoid the foreign live components getting attacked by the immune system [95, 96]. Artificial Ovaries, a self-assembled human theca and granulosa cell microtissue-based artificial human ovary can be used for IVM and further studies in oocyte toxicology. Artificial bladders, autologous living substitutes that are laboratory-grown [42]. Using microtissues that are self assembled created via 3D Petri dish technology, this project can combat complications regarding early menopause while also developing a system that can study

the effects environmental toxins have on folliculogenesis [97-99].

## 4. Discussion

Overall, none of the technologies mentioned above are perfected or have the capability of replacing organ transplantation entirely just yet. Nevertheless, their development give us hope for the future of organ replacement as they can help eliminate many of the issues that come with organ transplantation and further research might help develop these technologies onwards, rid of their limitations and risks for a better future regarding organ replacement methods that can potentially save more lives and improve the wellbeing of patients.

## 5. Conclusion

Today, the transplantation of organs' demands are much larger than the supply of available human organs and is estimated and expected to grow dramatically in the following two-three decades, which is the suggested time required to create innovative technologies according to the history of organ transplantation. Moreover, despite medicine and public policy's advances, many are doubtful that the human organ supply can be kept up with it's demand, implying that the urgency of developing alternative approaches will continue to grow. Organs generated in some fashion from stem cells obtained from the patient appear to be the most apparent, if not fully mature, answer. Even with the obstacles that have been identified and some that haven't been discovered, we are confident that a safer and more reliable method for producing organ replacements or human organs that are functional will be discovered. It is possible that society may not be able or willing to absorb the high price of producing stem cells for each and every individual that needs treatment, encouraging stem cells to form organs to implant them in the growing numbers of an aging population that come with cancer,failure of organs, or other conditions that may be lethal. The generation and testing of personalized pluripotent stem cells, growing them to the size of a liver or kidney for the purpose of implanting them will be significantly more pricey than allogeneic organ transplantation, even with the possibility of eliminating the need for ongoing immunosuppression. We believe that this issue will either rekindle enthusiasm for xenotransplantation or force the transplant community to confront the ethical dilemmas associated with healthcare rationing.

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