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Integrating Bioprinted Organs into Our Healthcare System

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Introduction

Every day, seventeen people in the United States die waiting for an organ transplant. Every nine minutes, the transplant waitlist becomes one name longer. Every year, 40,000 patients undergo transplant surgery (U.S. Government Information on Organ Donation and Transplantation, 2020). What if the 100,000 people in the United States currently waiting for an organ transplant never had to add their name to the list?

The idea of making a transplantable organ may seem more plausible as a science fiction novel's plot line than a blooming global industry. Yet estimates of personalized, bioprinted organs reaching the operating table range from 10 to 50+ years (Hunsberger, et al., 2016; Lewis, 2017). As the possibility of bioprinted organs for transplantation increasingly becomes a reality, society needs to be prepared. Currently, 50% of organ transplants are rejected within 10 years (University of Pittsburg, 2017). Bioprinted organs grown from a patient's cells could eliminate not only a lengthy transplant waitlist, but also the risks of rejection and the burden of a lifetime of anti-rejection medication. As the technology improves, organs manufactured through bioprinting are likely to not only be more widely available but also more affordable compared to the current situation: $1,664,000 for a heart transplant with an average wait time 213 days and $442,500 for a kidney transplant with an average wait time of 685 days (Scott, 2020). Beyond human applications, bioprinted organs also have applications as more ethical alternatives to the 25 million animals used in U.S. research laboratories each year (Humane Society, 2020).

Bringing bioprinted organs into society thoughtfully has the potential to improve the quality of life and save the lives of hundreds of thousands of people. We need to develop a plan and begin preparations for a new transplant system while maintaining the current one until bioprinting becomes viable, safe, and available. The current framework for organ transplantation in the United States and presence of transitional

technologies will help inform policy surrounding bioprinted organs. But implementation will require discussion about altering the National Transplant Act, FDA classification, medical precedents, insurance coverage mandates, patents, and the process of phasing in bioprinted organs while phasing out the transplant waitlist. Proactive alterations to our current organ transplant system will allow for the rapid integration of a new biotechnology into society. This paper will cover an overview of the bioprinting process, current companies and research, the legal landscape, and clinical translation. Finally, it will provide a vision of how bioprinting could serve in tandem with our current transplant system.

Bioprinting

Bioprinting falls under the umbrella of 3D printing or additive manufacturing, a process in which layers of biological material are stacked to form a structure (Murphy, et al., 2014). The applications of 3D printer biological structures in the clinical setting are exciting but challenging. To produce an entire organ, the ECM, or extracellular matrix, must be replicated along with different cell types, vasculature, and more (Murphy, et al., 2014). Bioprinting requires precise attention to both the macro and micro scales. Producing a bioprinted organ consists of three stages: pre-processing, processing, and post-processing (Vijayavenkataraman, et al., 2017).

During pre-processing, the patient undergoes imaging such as MRI, CT, or ultrasound. The scan is then used to create a digital 3D model which is sliced and formatted to be compatible with a 3D printer. The use of clinical imaging allows for patient-specific replication tissue distribution and geometry (Mandrycky, et al., 2016).

In the processing stage, sampled patient cells are cultured and mixed with hydrogel or other biomaterials to create a cell-laden bioink (Vijayavenkataraman, et al., 2017). Achieving the correct mechanical and chemical properties of the bioink is essential for successful printing. Customizable properties of the hydrogel include printability, crosslinkability, and biocompatibility.

Printability directly correlates with surface tension: the surface tension of the hydrogel or other supporting structure influences cell attachment and development (Mandrycky, et al., 2016). The hydrogel must achieve enough vertical tension to create a 3D structure while maintaining contact with the substrate. The ability of materials to be crosslinked is intertwined with printability. In order to be used as an ink, the material needs to be in a liquid form, but post-printing, it must become a scaffolded structure strong enough to support cell growth and overall organ maturation. Therefore, certain crosslinkable polymers must be used. (Vijayavenkataraman, et al., 2017). Cells can be seeded into a scaffold after printing is complete, or bioink can be mixed with living cells and directly printed into a structure (Murphy, et al. 2014).

Additionally, biocompatibility is necessary for any *in vivo* application. Materials used during bioprinting must be an acceptable environment for cell proliferation and bind with the cells. After transplantation, the bioprinted organ should fuse with neighboring tissue, so the hydrogel scaffold must degrade or incorporate into the extracellular matrix of the cells and be safe for the human body (Murphy, et al. 2014). The bioprinter can then produce the organ using the patient-specific bioink and digital file. In the final stage, post-processing, the organ is incubated to allow for tissue maturation and transported for transplantation or other applications (Vijayavenkataraman, et al., 2017).

Akin to the variety of office printers available, tissue bioprinters come in several different types such as inkjet, microextrusion, and laser-assisted (Vijayavenkataraman, et al., 2017).

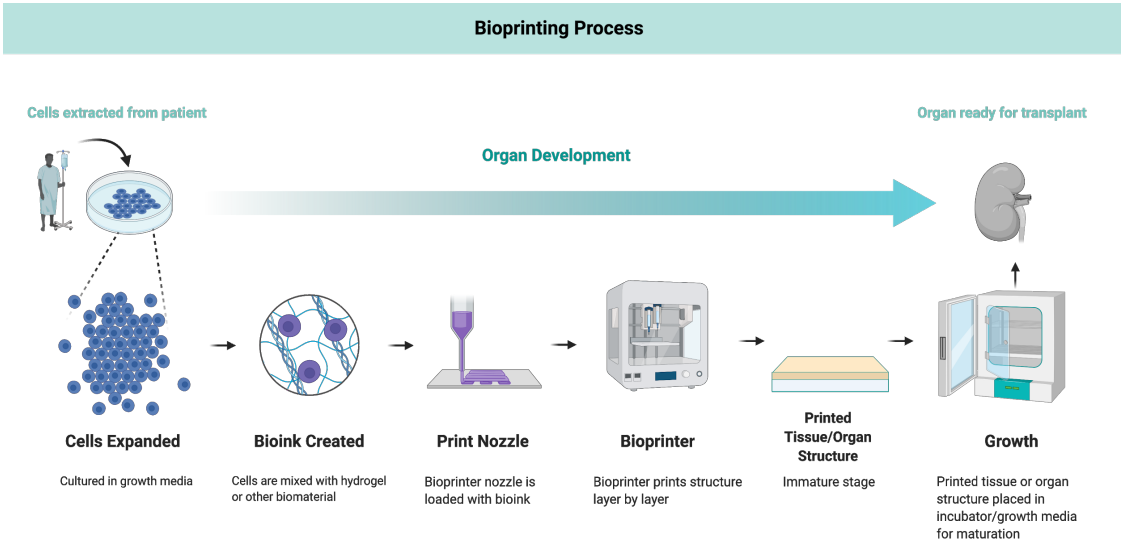

FIGURE 1: Bioprinting process

Extrusion printing occurs by forcing filaments through a nozzle to produce the 3D structure. This process involves direct contact between the nozzle and bioink--a combination of cells and carrier material (Smith, 2015). Alternatively, thermal ink-jet printing is a contactless process during which the print head heats up and uses compressed air to push regulated ink droplets through the nozzle (Jose, et al., 2016; Smith, 2015). All printers are guided by the digital file (CAD model) developed from patient scans to allow for ideal fit to the patient's body.

One alternative approach to 3D bioprinting is called *in vivo* printing, during which the biomaterial and cells are placed directly into the patient. Murphy, et al. successfully *in vivo* bioprinted skin onto burns (Murphy, et al., 2014). Although limited by the speed of printers, this technology could improve incision healing times post surgery.

The overall pipeline of a bioprinted organ, described in figure 2, would follow this sequence:

1) Patient organ is imaged (MRI/CT) and digital file is created
2) Organ is printed using cell infused bioink
3) Organ placed into an incubator to cultivate cells
4) Organ is transplanted into the patient

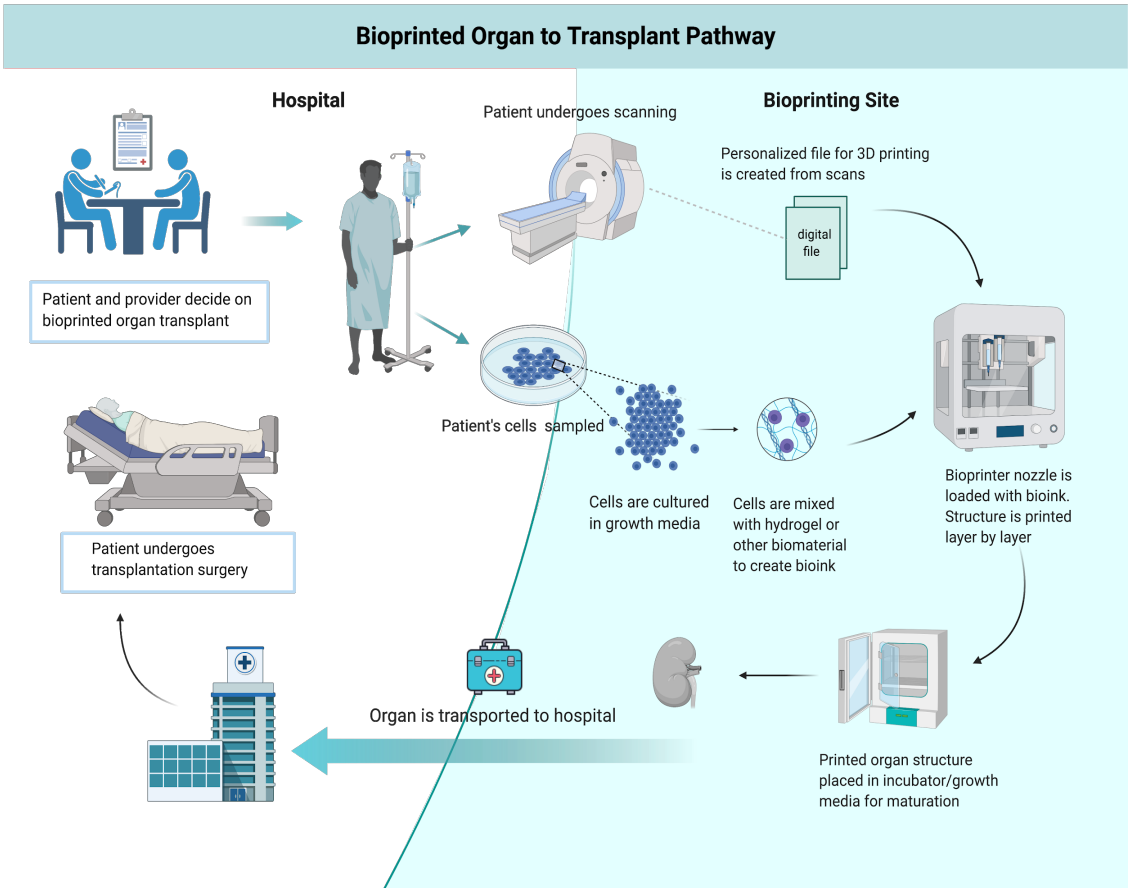

FIGURE 2: Bioprinted Organ to Transplant Pathway

A patient receiving a bioprinted organ transplant will likely go through the process depicted in figure 2. The patient will begin their transplant process after consulting with a medical provider. They will then undergo scanning and have their cells sampled. This could occur at either the hospital or bioprinting site (company) depending on hospital resources, location, patient mobility, and other factors. The scans and cells will be used to create the organ. This will likely be done using robotic systems as bioprinting companies scale. Finally, the organ will be transported from the bioprinting site to the hospital for the patient's transplant surgery.

Existing Companies

119 established companies are currently active in the bioprinting field worldwide (Listek, 2020). The leading company in the U.S. is Organovo, which focuses on commercializing printed tissues and their bioprinter *NovoGen MMX* (Jose, et al., 2016). In 2015, Organovo began a partnership with beauty company L'Oreal to create 3D bioprinted skin. L'Oreal plans to use the skin as animal replacement for product testing and development. CELLINK, founded in 2016, was the first company to offer a universal bioink product. Researchers can purchase the bioink online and then add their own focuses on eliminating animal testing and produces bioprinters and materials for researchers and healthcare providers (Listek, 2020). They sell a universal bioink gel designed for researchers to mix with cells along with a range of bioprinters and bioprinting products. Canadian company Aspect Biosystems primarily on producing skin but recently partnered with Johnson & Johnson to work on producing cartilage (J. (n.d.), 2017). They aim to create an artificial meniscus, a growing need in orthopedics. Cyfuse Biomedical ("Cell Fusion Future"), a Japanese company, is developing an innovative scaffold-free technology based on cell fusion. Cyfuse has two bioprinters on the market that utilize their needle array technology. Other companies focus on applications from cosmetic and reconstructive (TeVido Biodevices) to skeletal and bone (TRS), to improving the 3D printing technology itself (Jose, et al., 2016). Bioprinters have even been implemented in COVID-19 research to create human tissue and organoids for drug testing (Jose, et al., 2016).

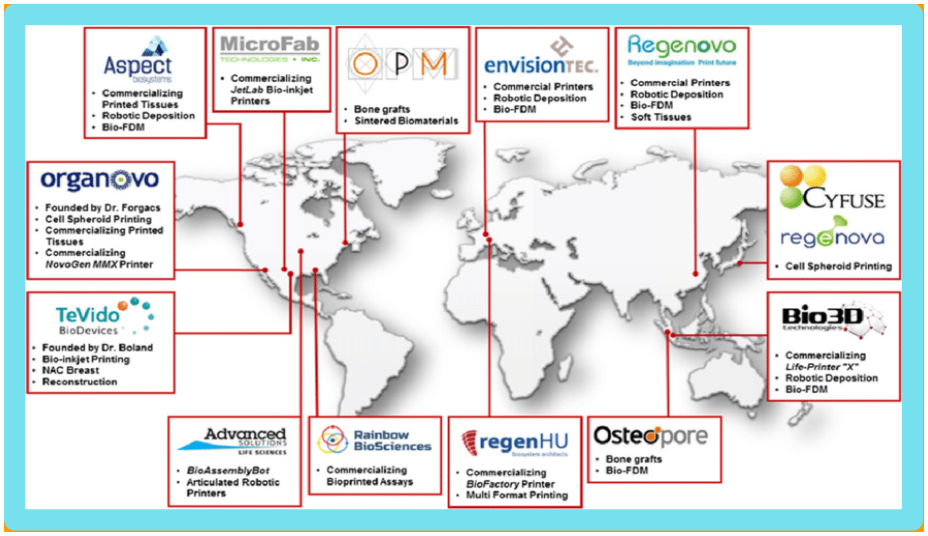

FIGURE 3: Landscape of Bioprinting Companies (Jose, et al., 2016).

Medical Precedent: Scaffolded Bladders

Currently, the only successfully bioprinted and transplanted human organ is the bladder. Dr. Anthony Atala, a leading researcher in regenerative medicine, implanted seven patients suffering from spina bifida with an

engineered bladder (Atala et al., 2006, p.1243). The bladders were created using the method of a biodegradable scaffold. This scaffold was then seeded with cultured urothelial and muscle cells from each patient's bladder biopsy (Atala et al., 2006, p.1243). The transplants have been successful for more than a decade. Unfortunately, Tengion Inc, the company conducting the clinical trials for these bladders, filed for Chapter 7 bankruptcy in 2014 (Clinicaltrials.gov, 2014). These autologous bladders serve as an exciting proof of concept and successful small clinical trial, but did not proceed far enough to shed light on what issuance and commercialization may look like for bioprinted organs. In recent news, printing company Poietis announced preparations for the first clinical trial of bioprinted skin in February of 2020 (Poietis, 2020). As will be discussed later in this paper, simpler bioprinted structures will likely reach the market decades earlier than complex organs.

The bioprinting market is projected to reach a startling $4.2 billion by 2027 (Grand View Research, 2020). As the industry expands, proactive regulation and preparation for incorporation into the healthcare system are necessary. Issues surrounding commercialization include current organ transplant laws, patentability and intellectual property of the technology, classification of bioprinted organs under FDA as medical devices or biologics, liability and safety concerns. All of these factors will play into how bioprinted organs are integrated into the transplant system.

Current Organ Transplant Laws

We need to determine what legal changes will be necessary for bioprinted organs to be incorporated into the healthcare landscape. The current organ transplant system in the United States is rooted within the National Organ Transplant Act (NOTA), which was approved in 1984. Motivations behind NOTA's enactment included addressing the critical national organ shortage through an equitable allocation system and preventing exploitation of donors in black market sales (National Academies of Sciences, 2017). The prohibition stated in NOTA is that:

> It shall be unlawful for any person to knowingly acquire, receive, or otherwise transfer any human organ for valuable consideration for use in human transplantation if the transfer affects interstate commerce. The preceding sentence does not apply with respect to human organ paired donation (NOTA; P.L. 98-507).

The code goes on to define human organ as "the human (including fetal) kidney, liver, heart, lung, pancreas, bone marrow, cornea, eye, bone, and skin or any subpart thereof and any other human organ (or any subpart thereof, including that derived from a fetus) specified by the Secretary of Health and Human Services by regulation" (NOTA; P.L. 98-507). The debate surrounding whether NOTA will apply to bioprinted organs or not centers around what counts as a human organ. This is not clearly clarified

within the law, and these uncertainties need to be addressed to allow bioprinted organs to reach the market. If bioprinted organs are considered human, this could happen through alteration of NOTA or the regulation provision.

If we explore the concept of bioprinted organs as not human, therefore escaping regulation by NOTA, the conversation involves the construction of the organ. It could be argued that any organ not grown solely in a body is inhuman. We must also consider that bioprinted organs are not entirely made up of biological products. A major factor in the composition of bioprinted organs are biomaterials, such as in the form of scaffolds or hydrogels for bioink (Jacobson, 2016). Does the addition of these products dehumanize the bioprinted organ? Organs altered through the addition of medical devices are still considered human (NOTA; P.L. 98-507). Complicating this conversation is the fact that most bioprinted organ scaffolds and materials are designed to biodegrade as the cells form into the desired shape (NOTA; P.L. 98-507). What materials, compository proportion, and maturation process is required for human organ classification is an area that should be clarified and adjusted within NOTA. The court needs to decide if the definition of human organ extends to a human created organ. Classifying bioprinted organs as human organs subject to NOTA would prohibit their commercial sale.

NOTA could be modified to state that "The preceding sentence does not apply with respect to human organ paired donation *or organs created through bioprinting or similar processes*." This would dually maintain the illegality of selling organs interpersonally while ensuring that bioprinted organs can be used in a clinical setting. From an ethical perspective, the motivations behind NOTA's creation in increasing availability of organs and preventing commercial organ sales apply differently to bioprinted organs. The risk of exploitation of donors is eliminated as well as supply shortage issues, therefore it could be argued NOTA is not necessary for bioprinted organs. NOTA does allow financial compensation for transplant surgeons, hospitals, transporters, and organ procurement organizations (OPOs) (National Academies of Sciences, 2017). A more unlikely path would be to allow bioprinting companies to be classified as OPOs, as they would replace the role of existing OPOs in the bioprinted transplant pathway. Through either approach, proactive amendment of NOTA would allow for faster integration of bioprinted organs into society from a legal standpoint.

The FDA

If bioprinted organs are not covered under NOTA, their regulation will fall under the FDA as either a medical device or biologic. In the 2017 document Technical Considerations for Additive Manufactured Medical Devices, the FDA Center for Devices and Radiological Health explicitly states that:

> This guidance does not address the use or incorporation of biological, cellular, or tissue-based products in AM [additive manufacturing]. Biological, cellular or tissue-based products manufactured using AM technology may necessitate additional regulatory and manufacturing process considerations and/or different regulatory pathways. Therefore, AM questions pertaining to biologics, cells or tissue products should be directed to the Center for Biologics Evaluation and Research (CBER) (FDA, 2017).

The AM (additive manufacturing) document FDA released therefore suggests that bioprinted organs not only will need modified regulatory pathways, but likely will not be considered a medical device but rather a biological product covered by CBER. Despite the FDA's directive, CBER has not yet issued any guidance regarding 3D bioprinting, although cellular therapies fall under their regulatory responsibilities (Gilbert, et al., 2017). Granted, the FDA has not yet had to face bioprinted organ regulation as a near term issue.

Attempting to box bioprinted organs into the existing FDA classification system is difficult because they are a hybrid innovation. Section 351 of the Public Health Service (PHS) Act defines a biological product as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein or analogous product, . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." The bioink and culture medias used in the production of bioprinted organs will contain protein, suggesting that bioprinted organs would be classified as biological components. But, they also contain non-biological components, such as hydrogel. The FDA has regulated silicone hydrogels for scar management as a class I devices (FDA). Bioprinted organs are highly individualized and created on a custom basis, similar to the FDA approved biologic CAR-T cell therapy. It is most likely that bioprinted organs will be regulated as biological products, yet their future approval by the FDA will represent increasingly hybridized medical innovations that do not fit perfectly within our existing classification systems.

Another question related to CBER's regulation of bioprinted organs is whether UNOS will also be involved. Likely, UNOS will continue to manage the natural organ network and transplant waitlist, but bioprinted organs will be transferred in a direct relationship between printing companies and hospitals.

Patents and Intellectual Property

Can bioprinted organs be patented? Tran et al. pose this question in "Patenting Bioprinting," in which they propose a middle ground solution: allowing patents for process claims but not product claims (Tran, 2015). The Leahy-Smith America Invents Act states "no patent may issue on a

claim directed to or encompassing a human organism" (Leah-Smith Act, 2012). This relates to the fundamental question raised when discussing NOTA and FDA classification of whether bioprinted organs are in fact human. To issue a patent, bioprinted human organs must be considered separate from human organisms. Notably, the Leahy-Smith Act does not apply to non-human animals, for which bioprinting could be patentable regardless.

Considering bioprinted organs implants would allow them to be patentable despite the Leahy-Smith Act. Tran et al. use the example of U.S. Patent No. 8,394,141, which "claims an implant formed from 'fibers of defatted, shredded, allogeneic human tissue' including a 'tendon, fascia, ligament, or dermis' and a 'growth factor' (to induce cell growth)" (Tran, 2015). Since bioprinted organs will most likely be regulated as biological products by the FDA rather than devices, implant classification seems unlikely.

Apart from organs themselves, bioprinting process claims are likely to be allowed. Existing method claims that may serve as a precedent for bioprinting include the following: U.S. Patent No. 7,051,654 claims a method of "forming an array of viable cells" and U.S. Patent No. 8,691,974 claims a method of "producing 3-D nano-cellulose based structures" (Tran, 2015). The printing of the organ may be patentable even if the printed product is not. Atala filed a provisional patent on his technology for engineered bladders (which has since expired) directed to the "methods and devices for the reconstruction, repair, augmentation or replacement of laminarily organized luminal organs or tissue structures in a patient in need of such treatment" (Atala, 2003). The focus of Atala's patent on the methods and device shapes an important precedent for approaching the patenting of tissue engineered and bioprinted products.

Discussing whether bioprinted organs should be patented at all brings up arguments for innovation and incentives that are applicable to bioprinted organs. As the technology makes strides in its marathon to functioning transplants, patentability could provide an extra push. Contrarily, patentability might also increase prices, potentially furthering transplant inequity. The compromise of allowing patents for printing process claims but not product claims provides a grounding point as bioprinting advances.

Insurance Coverage

Insurance coverage is key to making bioprinted organs accessible and equitable. In 2016, Japan's Social Insurance Medical Council announced that the national health insurance will pay for 3D printed organ models for medical treatments and surgeries (Open BioMedical Initiative, 2016). This decision will provide care to Japanese citizens regardless of economic status. As no organs are currently available this likely served as an advance action to encourage development and drive innovation and acceptance of the technology.

Providing government coverage for bioprinted transplants is essential to preventing the widening of the healthcare inequity gap. The current costs of transplantation are massive and inaccessible for the uninsured (Bently, 2020). Medicare currently covers services for heart, lung, kidney, pancreas, intestine, and liver organ transplants. Medicaid coverage varies by state with most requiring prior approval; California covers bone marrow, heart, kidney, liver, small bowel, lung, and pancreas transplants (CA.gov Medicare Reimbursements). Hopefully, Medicare and Medicaid will extend coverage to bioprinted organs once the technology reaches clinical translation.

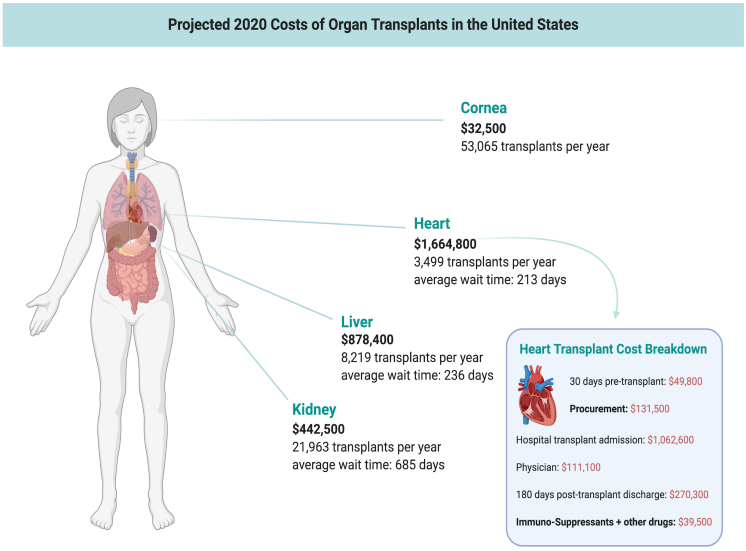

FIGURE 4: Projected 2020 Costs of Organ Transplants in the U.S

The majority of transplant cost comes from hospital facility charges for the transplant (Bently, 2020). Costs of immuno-suppressants and eventually organ procurement will probably be lower for bioprinted organs, but the overall expense of bioprinted organ transplantation will remain high. In time, coverage will likely be in the interest of all insurance companies due to the cost effectiveness of bioprinted organs--they will have lower rejection rates and associated lower costs, and likely, as the technology improves, lowered production costs. Additionally, the wait time will be significantly decreased, allowing for faster access to care for all. If bioprinted transplants are not covered by insurance, there could be damaging social equity effects where the wealthy could afford personalized organs, the poor would be left to receive natural organs from the transplant list, and the uninsured would have access to neither system.

Liability issues for bioprinting are embedded within the discussion of insurance coverage. Will the printing company hold responsibility for complications? The surgeon? The patient themselves, for donating the

cells? These issues will come down to specific cases, and it may be difficult to determine the direct cause of complications.

Clinical Translation

One of the first steps in the incorporation of bioprinted organs into our healthcare system will be the process of clinical translation. Due to both the invasiveness and patient specificity of bioprinted organs, this will be difficult and time consuming. Individual components of the manufactured organ, including scaffold and bioink materials will need to be tested for long term biocompatibility (Vijayavenkataraman, et al., 2017). Although a transplant may be reversible, lasting effects from a trial procedure that are ultimately damaging to the participant may not be (Vijayavenkataraman, et al., 2017). Therefore, despite the irony that bioprinted organs will reduce need for animal testing, in order to ensure their safety, significant preclinical testing on large animals will be necessary.

During clinical trials, participants with high and low numbers of comorbidities (the presence of multiple diseases) should be included in order to obtain the most accurate data (Vijayavenkataraman, et al., 2017). Most importantly, the trial participants must have informed consent. Preliminary trial participants may be people who have no other accepted clinical options: for example, a woman who has rejected a heart transplant multiple times and whose doctors believe could benefit from an organ with lower rejection risk. Additionally, studies should be conducted comparing patient outcomes with natural organ donation and bioprinted organs. Maintaining a global database of all pre-clinical and clinical trials will be important to making decisions about safety, efficacy, and when the time is right to transition bioprinted organs into a standard care option (Vijayavenkataraman, et al., 2017).

An important consideration is that bioprinted organs will reach translation at different rates due to complexity. A major challenge in bioprinting is vascularization: recreating the intricate vascular network of arteries, veins, and capillaries that supply the organ with oxygen and nutrients (Murphy, et al., 2020). Vascularization has only been accomplished for tissues a few millimeters thick. Approaches to address the challenge of vascularization include creating microchannels and patterning cells to facilitate vascular development (Murphy, et al., 2020). Because of the difficulty of vascularization, flat tissues such as skin are the most feasible to bioprint and solid organs are the most complex. Two clinically relevant 3D bioprinted tissues with the potential to reach patients first are skin and cartilage.

Skin has the advantage of being a very thin organ structure (2.5mm), making vascularization easier. Cell procurement is also more feasible for skin (Murphy, et al., 2020). 100 square centimeters of bilayered skin can be printed in approximately a half hour using fibroblasts and keratinocytes (major skin cell types) procured from skin biopsies (Murphy, et al., 2020). There is great need for the application of

bioprinted skin in wound healing as approximately 2% of the U.S. population is affected by chronic wounds (Sen, et al. 2019).

Cartilage is an avascular and aneural tissue, a simplicity that makes it intriguing for bioprinting. The challenge with cartilaginous tissue is its zonal organization (Murphy, et al., 2020). Cartilage has several layers (superficial zone, middle zone, deep zone, calcified). Each of these zones possess separate cell and extracellular matrix arrangements. Researchers have harvested chondrocytes (cartilage's only cell type) from each zone and deposit them in hydrogel, among other approaches (Murphy, et al., 2020). Bioprinted cartilage could be used in a variety of areas of the body from ears to as an osteoarthritis therapy, a condition that affects 32.5 million U.S. adults (CDC).

More complex bioprinted solid organ and tissue types will eventually follow skin, cartilage, and bladders. Amongst the most difficult organs to produce are the kidney and heart due to complex extracellular matrices and vasculature. The arrival of a viable bioprinted kidney will revolutionize the field of transplantation, as the vast majority of the transplant waitlist is made up of patients awaiting kidneys.

Coexistence of Transplant Waitlist and Bioprinted Organs

Since bioprinted organs will phase into our healthcare system one organ type at a time, there will be a significant period of time of two parallel organ transplant systems. The first will be the existing system of a UNOS moderated waitlist. This care option will continue to exist for all organs that have not yet been successfully bioprinted and for patients with religious or moral objections to bioprinting. Acting in conjunction with the present system, the bioprinting option will especially serve patients with high risk or history of rejection. It will also be especially used in areas or populations with low rates of donation of natural organs. The UNOS system will slowly phase out as more bioprinted replacements become available. Eventually, natural organ donation will be virtually obsolete as the bioprinted system becomes the sole provider due to less risk of rejection. In the future, it may be possible to maintain a small stock of bioprinted organs in or nearby hospitals for trauma cases if the technology does not reach a fast-enough printing and maturation timeline. In summary, as bioprinted organs phase in and replace natural organ donation, both systems will exist, until all organs are available via bioprinting and the regular natural organ transplant list is no longer necessary.

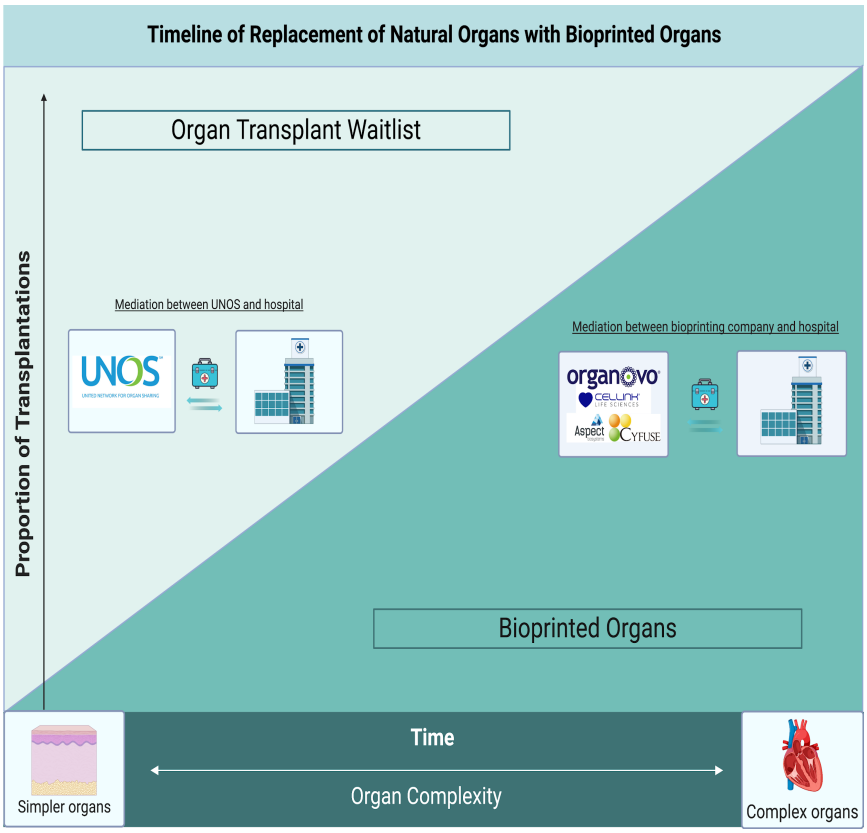

FIGURE 5: Phase in of Bioprinted Organs.

Conclusion

As the technology for bioprinted organs continues to advance, creation of a plan and legal structure for implementation is essential. Issues surrounding the implementation of bioprinted organs into our transplant system include NOTA, FDA classification, patents, insurance coverage, clinical translation, and parallel systems of natural transplant waitlist and bioprinted organs. More simple organ structures such as skin and bladders will likely phase in first and complex structures will continue to rely on the waitlist. The balance of use between the waitlist system and bioprinted organs will likely shift over time, until eventually, the waitlist system becomes obsolete as complex bioprinted organs become widely available and the maturation technology develops to a sufficiently rapid stage. Beyond organ transplants, there are exciting opportunities for bioprinting in areas such as *in vivo* drug testing, which would reduce animal testing and improve the speed andefficacy of pharmaceutical pipeline, and surgeries for transgender patients. We must proactively ensure the equitable integration of personalized bioprinted organs into our healthcare system to improve quality of life and save lives. Preparing for the arrival of this incredible technology is essential so that, in Dr. Atala's words, people on the national transplant list do not have to wait "for someone to die so they can live" (Parson, 2006).

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