

ORGAN BIOPRINTING: A CLOSER LOOK AT ETHICS AND POLICIES

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I. ORGAN BIOPRINTING

Organ transplantation is a currently accepted treatment modality for end-organ failure; however, donor organs are in severe short supply.¹ According to the latest data from the U.S. Department of Health and Human Services, an average of twenty-one people die daily due to lack of availability of donor organs for transplantation.² With modern technology, better health care, and an increase in life expectancy, there will be a considerable increase in the necessity for donor organs. Progress in the areas of tissue engineering and regenerative medicine is promising and may help reduce this growing gap in demand and supply of donor organs by enabling development of biological substitutes that restore, maintain, or improve tissue or whole organ function. In the last three decades, tissue engineering has evolved as a multidisciplinary field; it aims to build biological substitutes that mimic native tissue and can be used to replace damaged tissues or restore compromised organs.³ Conventionally, tissue engineering follows a top-down approach that involves taking a small biopsy from a patient, isolating cells from the biopsy, expanding cells, and seeding them on a natural or synthetic scaffold.⁴ The cells

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1. *See infra* Figure 1.

2. *The Need Is Real: Data*, U.S. DEP'T HEALTH & HUM. SERVICES, <http://www.organdonor.gov/about/data.html> (last visited Mar. 18, 2015).

3. Ibrahim T. Ozbolat & Yin Yu, *Bioprinting Toward Organ Fabrication: Challenges and Future Trends*, 60 IEEE TRANSACTIONS ON BIOMED. ENGINEERING. 691, 691 (2013).

4. *Id.* at 692–93, fig.2; *see infra* Figure 2.

proliferate and differentiate in the scaffold, and the resulting tissue construct is allowed to mature in a bioreactor before it is used for transplantation.⁵ This approach has resulted in significant clinical and research successes, including development of tissue engineered skin, cartilage, urinary bladder, trachea, and vagina.⁶ However, this approach is limited in terms of the precision and reproducibility that can be achieved, and this will affect the development of solid 3-D organs, which would require building more complex multicellular structures with vascular network integration.⁷

The technique of 3-D printing (originally named “stereolithography”), first described by Charles W. Hull in 1986, involved sequential printing of thin layers of a material and curing it with ultraviolet light to form a solid 3-D structure.⁸ This process was later used to build resin molds for developing 3-D scaffolds from biological materials.⁹ The development of solvent-free, aqueous-based systems has enabled printing of biological materials into 3-D scaffolds that could be used for transplantation with or without cells. Advances in cell and molecular biology and material science, in addition to those in 3-D printing techniques, have enabled the use of 3-D bioprinting for tissue engineering. 3-D bioprinting is a computer-aided manufacturing process that deposits living cells together with hydrogel-based scaffolds and allows for patterning of individual components of the tissue or organ thereby facilitating formation of complex tissue architecture.¹⁰ With over 121,000 Americans awaiting organ transplants,¹¹ the use of rapid prototyping techniques, such as bioprinting, would hasten the development of complex solid

5. Anthony Atala & Sean Vincent Murphy, *Organ Engineering—Combining Stem Cells, Biomaterials, and Bioreactors to Produce Bioengineered Organs for Transplantation*, 35 *BIOESSAYS* 160, 163–72 (2013), available at <http://onlinelibrary.wiley.com/doi/10.1002/bies.201200062/abstract>.

6. See generally Anthony Atala et al., *Engineering Complex Tissues*, 4 *SCI. TRANSLATIONAL MED.* 160rv12 (2012), available at <http://stm.sciencemag.org/content/4/160/160rv12>.

7. See generally Brian Derby, *Printing and Prototyping of Tissues and Scaffolds*, 338 *SCI.* 921 (2012) (discussing developments in the area of tissue engineering).

8. U.S. Patent No. 4,575,330 figs.1–8 (filed Mar. 11, 1986).

9. Anthony Atala & Sean Vincent Murphy, *3D Bioprinting of Tissues and Organs*, 32 *NAT. BIOTECHNOLOGY* 773, 773 (2014).

10. *Id.*

11. *The Need Is Real: Data, supra* note 2.

organs such as the kidney, heart, and liver.¹² 3-D bioprinting would help revolutionize tissue engineering and regenerative medicine by providing a technological platform that would facilitate precise, rapid, and reproducible fabrication of organs at a scale suitable for clinical use.

3-D bioprinting for fabricating biological constructs typically involves layer-by-layer addition of material on a pre-shaped supporting scaffold to build a 3-D tissue or organ construct with input from a computer-aided design (“CAD”) file.¹³ The scaffold is then dissolved, and the biological material is treated in a variety of ways to condition the cells and facilitate development of the organ construct.¹⁴ The placement of cells, materials, and growth signals required for tissue regeneration is precisely controlled using the CAD file so as to replicate the physiological organization.¹⁵ 3-D printing differs from conventional fabrication techniques because it does not involve removal or alteration of material during the object fabrication process. Using bioprinting, tissue or organ constructs can be tailor-fabricated by changes in the CAD file before printing, which reduces wastage and results in a cost-effective manufacturing process. Imaging of the target tissue in its environment is typically the first step in 3-D bioprinting.¹⁶ The choices of scaffold materials and cell source depend on the target tissue form and function. Common materials include synthetic or natural polymers and decellularized extracellular matrix (“ECM”).¹⁷ The cells could be from an allogeneic (different individual) or autologous (same individual) source and could be differentiated primary cells or undifferentiated pluripotent or multipotent stem cells.¹⁸ The printing process could be carried out on an inkjet, microextrusion, or laser-assisted printer.¹⁹ The bioprinted microtissues could subsequently be used

12. Ozbolat & Yu, *supra* note 3, at 691.

13. Atala & Murphy, *supra* note 9, at 777.

14. *Id.* at 778–79.

15. See generally Vladimir Mironov et al., *Organ Printing: Tissue Spheroids as Building Blocks*, 30 *BIOMATERIALS* 2164 (2009) (outlining the process to create).

16. See F. Guillemot et al., *High-Throughput Laser Printing of Cells and Biomaterials for Tissue Engineering*, 6 *ACTA BIOMATERIALIA* 2494, 2494 (2010).

17. Francoise Marga et al., *Toward Engineering Functional Organ Modules by Additive Manufacturing*, 4 *BIOFABRICATION* 1, 2 (2012).

18. Atala & Murphy, *supra* note 9, at 774, 781.

19. See, e.g., K. Iwami et al., *Bio Rapid Prototyping by Extruding/Aspirating/Refilling Thermoreversible Hydrogel*, 2 *BIOFABRICATION* 1, 1 (2010); Tao Xu et al., *Complex*

for *in vitro* or transplantation studies.²⁰ Depending on the application, the bioprinted tissue may need to be subjected to a period of maturation in a bioreactor before transplantation.²¹

II. APPLICATIONS OF BIOPRINTING

A. Biopharmaceutical Research and Development

Drug discovery is a very expensive and time consuming process. The average cost and time for developing a new drug are estimated to be around 1.8 billion dollars and around thirteen years, respectively.²² A number of companies, such as Organovo, Aspect Biosystems, and TeVido Biodevices, are developing 3-D bioprinted tissue models of liver and other organs that could be used for drug discovery and high-throughput toxicology testing.²³ Such applications are aimed at replacing animal testing of new drugs and enabling safer and more effective delivery of new drugs to the market at a much faster rate and lower cost.²⁴

B. Custom-Made Prosthetics and Implants

Custom-made prosthetics and implants are two areas where 3-D bioprinting directly affects the average person. Wearable prosthetics or implanted materials that are perfectly tailored to the anatomy at hand and provide structural support can be bioprinted for patient-specific parts using computerized tomography (“CT”) and 3-D scans from the respective parts.

Heterogeneous Tissue Constructs Containing Multiple Cell Types Prepared by Inkjet Printing Technology, 34 *BIOMATERIALS* 130, 131 (2013); Tao Xu et al., *Inkjet Printing of Viable Mammalian Cells*, 26 *BIOMATERIALS* 93, 93 (2005); see also Bertrand Guillotin et al., *Laser Assisted Bioprinting of Engineered Tissue with High Cell Density and Microscale Organization*, 31 *BIOMATERIALS* 7250, 7250 (2010) (demonstrating laser assisted bioprinting); Lauren Shor et al., *Precision Extruding Deposition (PED) Fabrication of Polycaprolactone (PCL) Scaffolds for Bone Tissue Engineering*, 1, 2 *BIOFABRICATION* 1 (2009) (demonstrating microextrusion printing).

20. Marga et al., *supra* note 17, at 3.

21. *Id.* at 1.

22. Steven M. Paul et al., *How To Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge*, 9 *NAT. REV. DRUG DISCOVERY* 203, 204 (2010).

23. Alexey Bersenev, *20 Bioprinting Companies To Watch*, *STEM CELL ESSAYS* (July 23, 2014), <http://stemcellassays.com/2014/07/20-bioprinting-companies>.

24. Giuseppe Orlando et al., *Will Regenerative Medicine Replace Transplantation?*, 3 *COLD SPRING HARBOR PERSP. MED.* 1, 12 (2013), available at <http://perspectivesinmedicine.cshlp.org/content/3/8/a015693.full.pdf+html>.

There have been a number of reports about the use of 3-D bioprinting to make prosthetics and implants.²⁵ Recently, in the Netherlands, a 3-D printed skull and 3-D printed jawbone were implanted into patients. In the United Kingdom, bioprinting was used for a massive facial reconstruction surgery.²⁶ In another case, surgeons in China rebuilt the skull of a patient, who lost half of his skull after falling from a building, with a customized 3-D printed titanium mesh that was molded in the shape of the part of his skull that was lost.²⁷ In some European countries, 3-D printed dental bridges have almost completely replaced precision castings for dental bridges, as it has become more time and cost-efficient to use intraoral scanners instead of impression trays for dental care.²⁸ Other applications of 3-D printing in prosthetics include cosmetic and bionic ears, noses, customized coverings for artificial limbs, and hearing aid shells.²⁹

C. Pre-Surgical Planning

Bioprinting technology is gaining acceptance in the development of clinical models representative of specific medical conditions for pre-surgical planning and medical training. Traditionally, surgeons learned on live pigs.³⁰ The advent of bioprinting has provided surgeons the opportunity to rehearse surgical procedures in realistically textured environments on anatomically precise 3-D printed molds generated from MRI and CT scans.³¹ The ability to practice on models of organs that

25. *Prosthetics*, BIOPRINTING WORLD, <http://bioprintingworld.com/category/prosthetics> (last visited Mar. 13, 2015).

26. Brooke Kaelin, *First 3D Printed Titanium Jaw Implant Successful*, 3D PRINTER WORLD (Aug. 16, 2013), <http://www.3dprinterworld.com/article/first-3d-printed-titanium-jaw-implant-successful>; see also Hywel Griffith, *Pioneering 3D Printing Reshapes Patient's Face in Wales*, BBC NEWS (Mar. 12, 2014), <http://www.bbc.com/news/uk-wales-26534408>.

27. Gunjan Sinha, *Cell Presses*, 32 NATURE BIOTECHNOLOGY 716, 719 (2014).

28. Robert Dehue, 3-D PRINTING TECHNIQUES FOR DENTAL PRODUCTS, <http://3dprinting.com/products/dental/3d-printing-dental-products> (last visited Mar. 26, 2015).

29. See, e.g., Manu S. Mannoor et al., *3d Printed Bionic Ears*, 13 NANO LETT 2634, 2635 (describing the printing of ears); *The Future of Prosthetics: 3D Printed Nose, Ear and Eye*, 3DERS (Nov. 8, 2013), <http://www.3ders.org/articles/20131108-the-future-of-prosthetics-3d-printed-nose-ear-and-eye.html> (describing the printing of ears, noses, and eyes).

30. Jameel Ali et al., *Teaching Emergency Surgical Skills for Trauma Resuscitation-Mechanical Simulator Versus Animal Model*, 2012 ISNR EMERGENCY MED. 1, 1 (2012).

31. Nicholas J. Mankovich et al., *Surgical Planning Using Three-Dimensional Imaging and Computer Modeling*, 27 OTOLARYNGOL CLINIC N. AM. 875, 878 (1994).

reproducibly simulate complex structures and individualized medical defects enables surgeons to practice specific procedures for specific patients before setting foot in the operating room. This would make life saving medical procedures faster, more efficient, and safer. Recently, there have been a number of reports describing how bioprinted models depicting specific clinical cases have been helpful in surgical planning and lead to life saving medical procedures.³²

Some examples of the use of 3-D printed models in surgical planning are described below. 3-D printed neuroanatomical models reflecting the relationship between a lesion and normal brain structures can be very helpful to neurosurgeons and provide an accurate representation of the intricate relationships between cranial nerves, vessels, cerebral structures, and skull architecture.³³ Such models help determine the safest surgical corridor, which otherwise would be difficult to predict solely using 2-D radiographic images.³⁴ 3-D printed liver models have been reportedly used by transplant surgeons in Kobe University Hospital in Japan to carve, with minimal tissue loss, a donor liver to fit the recipient's abdominal cavity.³⁵ A 3-D printed model of a calcified aorta has been used for surgical planning of plaque removal.³⁶ A premature infant's airway was reconstructed using 3-D printing to study aerosol drug delivery to the lungs.³⁷ In orthopedic surgeries, custom 3-D printed models of the patient's bones have been used to plan surgeries.³⁸

32. See, e.g., Damien Gayle, *Two-Year-Old Girl's Now Living a Normal Life After Pioneering Surgeons Use 3D Printer To Make Copy of Her Heart*, DAILY MAIL (Jan. 25, 2015, 6:22 PM), <http://www.dailymail.co.uk/health/article-2925771/Two-year-old-girl-s-living-normal-life-pioneering-surgeons-use-3D-printer-make-copy-heart.html> (examining doctors' use of 3-D models to plan complex heart surgery for small child); Karen Weintraub, *Off the 3-D Printer, Practice Parts for the Surgeon*, N.Y. TIMES (Jan. 26, 2015), http://www.nytimes.com/2015/01/27/science/off-the-3-d-printer-practice-parts-for-the-surgeon.html?_r=0 (explaining that 3-D printing allows unprecedented surgical planning and allowed doctors here to plan for a complex facial cleft surgery).

33. See Geraldine T. Klein, Yi Lu & Michael Y. Wang, *3D Printing and Neurosurgery—Ready for Prime Time?*, 80 WORLD NEUROSURGERY 233, 233–34 (2013).

34. *Id.*

35. *Id.* at 233.

36. Bethany C. Gross et al., *Evaluation of 3D Printing and Its Potential Impact on Biotechnology and the Chemical Sciences*, 86 ANALYTICAL CHEMISTRY 3240, 3247 (2014).

37. *Id.*

38. Matthew B. Hoy, *3D Printing: Making Things at the Library*, 32 MED. REFERENCE SERVICES Q. 94, 96 (2013).

III. BIOPRINTING SYSTEMS

A. Inkjet Bioprinting

Inkjet bioprinters are the most commonly used type of printer for nonbiological and biological applications and were modified versions of commercially available 2-D ink-based printers.³⁹ The main differences between bioprinters and commercially available 2-D printers are that the traditional 2-D ink in the cartridge is substituted with biological material and the paper is replaced with an electronically controlled elevator stage that controls the z-axis.⁴⁰ Inkjet printers use thermal or acoustic forces to eject drops of liquid onto a substrate that can support or become part of the final tissue construct.⁴¹ Some of the disadvantages of inkjet bioprinting include the fact that the biological material must be in liquid form to enable droplet formation; as a result, the printed liquid must then form a solid 3-D structure.⁴² Another limitation is the difficulty in achieving biologically relevant cell densities. Our research group and others have shown that this limitation could be addressed by using materials that can be crosslinked after deposition by printing using chemical, pH, or ultraviolet mechanisms.⁴³ Notwithstanding these drawbacks, inkjet-based bioprinters also offer advantages, including low cost, high resolution, high speed, and compatibility with many biological materials.⁴⁴

Our research group has successfully used inkjet bioprinters to bioprint functional skin, and others have demonstrated its use

39. See generally Tao Xu et al., *High-Throughput Production of Single-Cell Microparticles Using an Inkjet Printing Technology*, 130 J. MFG. SCI. ENGINEERING 21017 (2008); Tao Xu et al., *Characterization of Cell Constructs Generated With Inkjet Printing Technology Using In Vivo Magnetic Resonance Imaging*, 130 J. MFG. SCI. ENGINEERING 21013 (2008).

40. Tadashi Okamoto et al., *Microarray Fabrication with Covalent Attachment of DNA Using Bubble Jet Technology*, 18 NATURE BIOTECHNOLOGY 438, 438 (2008). The z-axis is the dimension added to the x- and y-axes.

41. Torsten Goldmann & Juan S. Gonzalez, *DNA-Printing: Utilization of a Standard Inkjet Printer for the Transfer of Nucleic Acids to Solid Supports*, 42 J. BIOCHEMICAL & BIOPHYSICAL METHODS 105, 106 (2000).

42. Atala & Murphy, *supra* note 9, at 776.

43. Saif Khalil & Wei Sun, *Biopolymer Deposition for Freeform Fabrication of Hydrogel Tissue Constructs*, 27 MATERIALS SCI. & ENGINEERING 469, 471 (2007); Sean V. Murphy et al., *Evaluation of Hydrogels for Bio-Printing Applications*, 101A J. BIOMEDICAL MATERIALS RES. 272, 277 (2012).

44. Atala & Murphy, *supra* note 9, at 776.

for printing cartilage *in situ*,⁴⁵ which demonstrates the potential use of these bioprinters in regenerating functional structures. They have also been used to fabricate bone constructs, which were further assessed for *in vivo* maturation and mineralization in rodent models.⁴⁶

B. Microextrusion Bioprinting

Microextrusion bioprinters are the most common and affordable nonbiological 3-D printers and typically consist of a temperature-controlled material handling and dispensing system and stage, a fiber-optic light source to illuminate the deposition area and for photo initiator activation, a video camera, and a piezoelectric humidifier.⁴⁷ Extrusion of material onto a substrate is robotically controlled, wherein continuous beads of material are deposited in two dimensions as directed by the CAD-CAM software.⁴⁸ A variety of materials are compatible with microextrusion printers, such as hydrogels, biocompatible copolymers, and cell spheroids.⁴⁹

The main advantage of microextrusion bioprinting technology is the ability to deposit very high cell densities, which is beneficial for tissue engineering of organs.⁵⁰ However, the cell viability following microextrusion bioprinting has been observed to be lower than that obtained using inkjet-based bioprinting, likely due to the shear stresses inflicted on cells in viscous fluids

45. Aleksander Skardal et al., *Bioprinted Amniotic Fluid-Derived Stem Cells Accelerate Healing of Large Skin Wounds*, 1 STEM CELLS TRANSL. MED. 792, 792–94 (2012); Xiaofeng Cui et al., *Direct Human Cartilage Repair Using Three-Dimensional Bioprinting Technology*, 18 TISSUE ENGINEERING PART A 1304, 1304 (2012).

46. Cynthia M. Smith et al., *Three-Dimensional BioAssembly Tool for Generating Viable Tissue-Engineered Constructs*, 10 TISSUE ENGINEERING 1566, 1567 (2004).

47. Nicola Jones, *The Print Revolution*, 487 NATURE 22, 22–23 (2012).

48. Carlos Chang et al., *Direct-Write Bioprinting Three-Dimensional Biohybrid Systems for Future Regenerative Therapies*, 98 J. BIOMEDICAL MATERIALS RES. PART B: APPLIED BIOMATERIALS 160, 163 (2011); Robert Chang et al., *Direct Cell Writing of 3D Microorgan for In Vitro Pharmacokinetic Model*, 14 TISSUE ENGINEERING PART C 157, 158 (2008); Natalja Fedorovich et al., *Evaluation of Photocrosslinked Lutrol Hydrogel for Tissue Printing Applications*, 10 BIOMACROMOLECULES 1689, 1691 (2009); Atala & Murphy, *supra* note 9, at 777.

49. Atala & Murphy, *supra* note 9, at 777.

50. *Id.*; see also Vladimir Mironov et al., *Organ Printing: from Bioprinter to Organ Biofabrication Line*, 22 CURRENT OPINION BIOTECH. 667, 670 (2011).

during the printing process.⁵¹ These bioprinters have been used to fabricate multiple tissue types, including aortic valves, branched vascular trees, and *in vitro* pharmacokinetic and tumor models.⁵² Although the fabrication time can be slow for high-resolution complex structures, constructs that range from clinically relevant tissue sizes down to micro-tissues in microfluidic chambers have been fabricated using microextrusion bioprinters.⁵³

C. Laser-Assisted Bioprinting

Laser-assisted bioprinting (“LAB”) is less common than inkjet or microextrusion bioprinting, but it is increasingly being used for tissue engineering applications. Typically, LAB consists of a pulsed laser beam; a focusing system; a ‘ribbon’ that has a donor transport support usually made from glass covered with a laser-energy-absorbing layer, such as gold or titanium; a layer of biological material, such as cells and-or hydrogel prepared in a liquid solution; and a receiving substrate facing the ribbon.⁵⁴ LAB functions by using focused laser pulses on the absorbing layer of the ribbon to generate a high-pressure bubble that propels cell-containing materials toward the collector substrate.⁵⁵ LAB can deposit cells at a density of up to 100 million cells per milliliter with microscale resolution of a single cell per drop; however, despite these advantages, the process is very time consuming because the high resolution of LAB requires rapid gelation kinetics to achieve high shape fidelity.⁵⁶ LAB is also costly, which is a concern for basic tissue-engineering research.⁵⁷

Fabrication of a cellularized skin construct using LAB demonstrates the potential of this system to print clinically

51. Atala & Murphy, *supra* note 9, at 777; see also K. Nair et al., *Characterization of Cell Viability During Bioprinting Processes*, 4 BIOTECH. J. 1168, 1174–75, fig.8 (2009).

52. Atala & Murphy, *supra* note 9, at 777.

53. *Id.*

54. Douglas B. Chrisey, *The Power of Direct Writing*, 289 SCIENCEMAG.ORG 879, 881 (2000); Fabien Guillemot et al., *Laser-Assisted Cell Printing: Principle, Physical Parameters Versus Cell Fate and Perspectives in Tissue Engineering*, 5 FUTURE MED. 507, 509 (2010).

55. Valentina Dinca et al., *Directed Three-Dimensional Patterning of Self-Assembled Peptide Fibrils*, 8 NANO LETTERS 538, 539 (2008).

56. Bertrand Guillotin et al., *Laser Assisted Bioprinting of Engineered Tissue with High Cell Density and Microscale Organization*, 31 BIOMATERIALS 7250, 7250 (2010).

57. Stefanie Michael et al., *Tissue Engineered Skin Substitutes Created by Laser-Assisted Bioprinting Form Skin-Like Structures in the Dorsal Skin Fold Chamber in Mice*, 8 PLOS ONE 1, 11 (2013).

relevant cell densities in a layered tissue construct.⁵⁸ Also, LAB has been used *in vivo* to deposit nano-hydroxyapatite in a mouse calvaria 3-D defect model, wherein a three millimeter diameter, 600 micrometer-deep calvarial hole was filled as a proof of concept.⁵⁹ Laser 3-D printing was recently used to fabricate a customized, non-cellular, bioresorbable tracheal splint that was implanted into an infant with tracheobronchomalacia.⁶⁰

IV. ETHICAL AND POLICY ISSUES

Organ bioprinting is a newer application of 3-D printing. We currently only have the technical capability to print micro-tissues; it will likely be a decade or more before we achieve the capability to commercially bioprint transplant size and compatible organs.⁶¹ The Food and Drug Administration (“FDA”) will evaluate all bioprinted tissues and organs for safety and effectiveness and assess the benefits and risks involved. A number of regulatory and legislative hurdles will need to be cleared before the first lab-printed kidney, liver, or heart implant becomes commercially available. Technological advancements in terms of software, more sophisticated bioprinters, and advances in tissue engineering and regenerative medicine technology are needed before the widespread application of bioprinting occurs. Regardless, there is a lack of public policy applicable to bioprinting.⁶² Some of the issues that should be taken into account when policies are developed for bioprinting are discussed below.

A. Cell Sourcing

During the bioprinting process it is expected that the cells will be exposed to different shear stresses and pressures, so it is essential that the cells used for bioprinting remain viable after printing and through *in vitro* tissue maturation and post-

58. Virginie Keriquel et al., *In Vivo Bioprinting for Computer- and Robotic- Assisted Medical Intervention: Preliminary Study in Mice*, 2 BIOFABRICATION 1, 2 (2010).

59. *Id.* at 2–3.

60. David A. Zopf et al., *Bioresorbable Airway Splint Created with a Three-Dimensional Printer*, 368 NEW ENGINEERING J. MED. 2043, 2043 (2013).

61. See, e.g., Young Joon Seol et al., *Bioprinting Technology and Its Applications*, 46 EUR. J. CARDIOTHORACIC SURGERY 342, 345, 347 (2014).

62. Jasper L. Tran, *To Bioprint or Not to Bioprint*, 17 N.C. J.L. & Tech. (forthcoming 2015), available at <http://ssrn.com/abstract=2562952>.

transplantation.⁶³ Typically, cells such as fibroblasts or transformed cell lines that are robust enough when exposed to such changes are used for bioprinting.⁶⁴ More efficient cell reprogramming and directed differentiation methods coupled with better cell culture techniques will help provide highly proliferative and robust cells that could be utilized for bioprinting.

Appropriate choice of cells for tissue or organ bioprinting is crucial to ensure proper function of the fabricated tissue or organ construct. Organs typically consist of multiple cell types, some of which serve specific functional or structural roles, while some others serve supportive roles.⁶⁵ Typically, bioprinting involves either deposition of multiple primary cell types into patterns that represent the native tissue or printing of stem cells, which would proliferate and differentiate into the required cell types.⁶⁶ The cells chosen for bioprinting should be able to maintain *in vivo* function under suitable conditions.⁶⁷

Rejection of the bioprinted tissue or organ by the recipient or host immune system is a potential problem that could be circumvented by using autologous cells.⁶⁸ Autologous cells for bioprinting could be isolated from tissue biopsies, generated by differentiation of autologous stem cells, or through reprogramming of adult cells to pluripotent stem cells (known as induced pluripotent stem cells or iPS cells).⁶⁹ When iPS cells are used in bioprinting, for example, to treat burn victims, sheets of iPS cells derived from healthy skin cells obtained from the burn victim can be bioprinted as a construct. These cells will grow and differentiate into skin cells, and then the construct will be transplanted to cover the wounded areas. The cells can also be directly bioprinted on the wounds.⁷⁰ However, use of iPS cells may not be possible if the health of the patient is compromised or the

63. Atala & Murphy, *supra* note 9, at 781.

64. *Id.*

65. *Id.*

66. *Id.*

67. *Id.*

68. Prajna Guha et al., *Lack of Immune Response to Differentiated Cells Derived from Syngenic Induced Pluripotent Stem Cells*, 12 CELL STEM CELL 407, 407–12 (2013).

69. Piyush Bajaj et al., *3D Biofabrication Strategies for Tissue Engineering and Regenerative Medicine*, 16 ANN. REV. BIOMEDICAL ENGINEERING 247, 250–53, tbl.1, fig.3 (2014).

70. Kyle W. Binder, *In Situ Bioprinting of the Skin* (May 2011) (unpublished Ph.D. dissertation, Wake Forest University) (on file with Wake Forest University library).

patient has certain genetic disorders, because the isolated cell types may not produce the desired function in the bioprinted construct.⁷¹ The use of embryonic stem cells for bioprinting is not very common due to the ethical concerns it raises, as these cells are obtained by destroying embryos.⁷² Also, primary cells are difficult to expand and culture in large numbers that could be used in bioprinting because they have finite lifespans.⁷³ Stem cells are a promising alternative due to their ability to proliferate without differentiating and their capability to generate multiple functional tissue-specific cell types. Embryonic stem cells and induced pluripotent stem cells are capable of indefinite self-renewal and have demonstrated their longevity by maintaining their undifferentiated state for over eighty passages.⁷⁴ The capacity of pluripotent stem cells to generate large numbers of cells highlights their potential for use in bioprinting applications. Stem cells from other sources such as bone marrow, fat, amniotic fluid, and placenta are believed to have a more limited multipotent differentiation potential, but are considered safer for clinical transplantation with the potential for autologous applications.⁷⁵ With established protocols for their isolation, expansion, and differentiation, mesenchymal stromal cells (“MSCs”) may also be a promising cell source for bioprinted constructs.⁷⁶ Clinically relevant numbers of MSCs have been successfully generated *in vitro* for clinical trials, and future advances in cell-culture techniques are likely to make use of other stem cell populations for bioprinting clinical applications a realistic possibility.⁷⁷

71. Guangjin Pan et al., *Somatic Cell Reprogramming for Regenerative Medicine: SCNT vs. iPS Cells*, 34 *BIOESSAYS* 472, 473 (2012).

72. Jennifer L. Olson et al., *Tissue Engineering: Current Strategies and Future Directions*, 47 *CHONNAM MED. J.* 1, 3 (2011).

73. Goberdhan P. Dimri et al., *A Biomarker That Identifies Senescent Human Cells in Culture and in Aging Skin In Vivo*, 92 *CELL BIOLOGY* 9363, 9363 (1995).

74. Benjamin E. Reubinoff et al., *Embryonic Stem Cell Lines from Human Blastocysts: Somatic Differentiation In Vitro*, 18 *NAT. BIOTECHNOLOGY* 399, 399 (2000).

75. Atala & Murphy, *supra* note 9, at 781.

76. *Id.*

77. Walid Zaher et al., *An Update of Human Mesenchymal Stem Cell Biology and Their Clinical Use*, 88 *ARCHIVES TOXICOLOGY* 1069, 1070, 1076 (2014).

B. Cost and Reimbursement

Development in 3-D printing technologies is expected to revolutionize mass production of goods and make many of them cheaper and very accessible. However, there are several challenges that must be addressed before bioprinting of transplantable whole organs becomes a reality. Building complex functional tissue engineered organs through bioprinting will be expensive. Higher costs may lead to a possibility that only those who can afford the technology receive it, rather than those who might need it more.⁷⁸ The availability of reimbursements will ensure broader access to potentially life-saving bioprinted technologies. If reimbursements are not provided, application of these products would be the privilege of few, and all benefits of publicly funded research would be accessible only to a very small section of the society.⁷⁹ Overall, cost would be a very critical factor in driving the use of this technology in personalized medicine.

C. Quality of Bioprinted Organs and Use of Cells from Same Species

Before bioprinted products become commercially available, a number of regulatory and legislative considerations need to be addressed. There is a risk that bioprinted organs and therapies could become commercially available before any hazards are adequately assessed. Mandatory and stringent tests for purity, identity, and stability need to be established. One of the fears highlighted in mass media regarding bioprinted organs is that the tissue-engineered organs may contain either autologous or allogeneic human cells or xenogeneic cells from other species.⁸⁰ Concerns with use of xenogeneic cells include: introduction of pathogenic agents, such as bacteria, viruses, and other infectious agents into humans; serious immunological problems xenogeneic cells may cause if they are not genetically altered; and the public acceptability of using cells of animal origin.⁸¹ Some people find the introduction of animal cells into the human body

78. Atala & Murphy, *supra* note 9, at 776–77, tbl.1.

79. *Id.* at 776–77.

80. Alex Faulkner et al., *Purity and the Dangers of Regenerative Medicine: Regulatory Innovation of Human Tissue-Engineered Technology*, 63 SOC. SCI. MED. 2277 *passim* (2006).

81. *Id.*; Marc R. Hammerman & Raffaello Cortesini, *Organogenesis and Tissue Engineering*, 12 TRANSPLANT IMMUNOLOGY 191, 191 (2004).

objectionable, while others reject the use of material from specific animal species on the basis of religious considerations.⁸² The use of allogeneic cells is also not completely problem free; these cells must be subjected to rigorous quality-control measures to assess for immunological compatibility and risks of potential disease transmission.⁸³ Regulatory and control mechanisms will be required to ensure that the cells used in the bioprinted tissue are of the best quality.

D. Translational Pathway—Pre-clinical Studies and Clinical Trials

Pre-clinical studies using 3-D bioprinted tissue should be appropriately conducted in suitable animal models. The obtained safety and efficacy results should justify progression to clinical trials. The clinical trials will need to be designed with care and rigor and conducted in a manner that protects the rights, interests, and welfare of the clinical trial participants.⁸⁴ Ethics considerations should aim to minimize the risks of harm by selecting and recruiting appropriate patient-subjects and should facilitate informed decision-making through the consent form and process.⁸⁵ Donors should be informed as fully as possible about future uses of their tissues or cells, and no tissue or cells should be used without the consent of the donor.⁸⁶ The consent forms should include complete details about the composition of the bioprinted or tissue engineered product, the process for its implantation, all conflicts of interest, and all potential outcomes and adverse events or effects.⁸⁷ These details should all be provided to the patients in a manner that they can fully comprehend. Because some aspects of these products and procedures are complex, unbiased patient advocates should be

82. Faulkner et al., *supra* note 80, at 2283–85.

83. Jonathan Black, *Thinking Twice About “Tissue Engineering,”* 16 IEEE ENGINEERING IN MED. & BIOLOGY MAG. 102, 102 (1997).

84. Nancy MP King & Jacob Perrin, *Ethical Issues in Stem Cell Research and Therapy*, 5 STEM CELL RES. THERAPY 85, 87 (2014), available at <http://stemcellres.com/content/5/4/85>.

85. *Id.*

86. M.B. Kapp, *Ethical and Legal Issues in Research Involving Human Subjects: Do You Want a Piece of Me?*, 59 J. CLINICAL PATHOLOGY 335, 337 (2006).

87. Doris A. Taylor et al., *Ethics of Bioengineering Organs and Tissues*, 14 EXPERT OPIN. BIOL. THER. 879, 881 (2014).

made available to patients.⁸⁸ This would facilitate fair, unbiased consultations before consent forms are signed. Other issues in terms of conducting clinical trials involving bioprinted organs should include opportunities for extensive cost-benefit assessments, clearly defined criteria for efficacy and safety of these tissues or organs, and long-term post trial follow-ups to review safety of the bioprinted organs.⁸⁹

Of similar importance is the need to protect the privacy of the donor, for example, through the anonymization of samples used in scientific research.⁹⁰ Free and unpaid donation should be the ideal behind policy legislation regulating the collection of cells or tissues. Another related issue of importance involves who has authority and ownership over cells that would be used in the tissue engineered organs.⁹¹ These rights may be necessary for allowing paid donation and the patenting of processes involving human cells, as well as the cells themselves.⁹² Clinical trials should be designed so that they contribute knowledge that could be generalized to a wider population.⁹³ Increased transparency, disclosure of information, and discussion of uncertainties regarding outcomes with clinical trial participants will also help in increasing patient safety and preventing use of unapproved or unproven treatment modalities.

E. Disease Modeling and Drug Discovery

3-D bioprinting holds great promise in terms of contributing to disease modeling and drug development research

88. *Id.*

89. Rob B.M. de Vries et al., *Ethical Aspects of Tissue Engineering: A Review*, 14 *TISSUE ENGINEERING PART B* 367, 369 (2008), available at <http://online.liebertpub.com/doi/pdf/10.1089/ten.teb.2008.0199> (describing the importance of privatizing umbilical cord blood donations).

90. Elena Salvaterra et al., *The Ethics of Cord Blood Banking in Light of Ownership, Informed Consent, and Solidarity*, 4 *CELL PRESERVATION TECH.* 91, 92 (2006), available at <http://online.liebertpub.com/doi/pdf/10.1089/cpt.2006.4.91>.

91. Wolfgang E. Thasler et al., *Charitable State-Controlled Foundation Human Tissue and Cell Research: Ethic and Legal Aspects in the Supply of Surgically Removed Human Tissue for Research in the Academic and Commercial Sector in Germany*, 4 *CELL TISSUE BANK* 49, 51 (2003).

92. Faulkner et al., *supra* note 80, at 2283; see generally Gareth Williams, *Patenting of Stem Cells*, 1 *REGENERATIVE MED.* 697 (2006).

93. Mette Ebbesen & Thomas G. Jensen, *Nanomedicine: Techniques, Potentials, and Ethical Implications*, 1 *J. BIOMED. BIOTECHNOLOGY* 1, 6 (2006), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1779503/pdf/JBB2006-51516.pdf>.

by significantly reducing costs and time involved.⁹⁴ Bioprinted tissue systems could help faster determination of toxicity and efficacy of specific treatments and enable tailor-assessment of drugs. The creation and use of disease-specific iPS cells in bioprinted tissues constitute essential components of disease modeling and drug discovery. Because iPS cells are derived from the somatic cells of identifiable individuals, disclosing to those individuals the intended or envisioned uses of iPS cells derived from the donated cells and obtaining the individuals' consent are critical for the creation and future use of bioprinted tissue systems developed using previous tissue samples.⁹⁵

F. Social Justice

Future efforts should be directed at reducing the cost of bioprinted tissues in order to reduce potential disparities in accessibility of bioprinted tissues when required as part of treatment. Scientific transparency in terms of data sharing and intellectual property interests of academic and industrial research partners also have significant justice implications for the field of organ bioprinting.⁹⁶ An important ethical issue that could arise with respect to the use of bioprinted tissue involves social justice; high costs of producing bioprinted tissue could lead to the possibility that it may only be available to affluent sections of society.⁹⁷ For example, organ donations are typically regulated through extensive waiting lists and are based on factors such as critical condition of the patient and how long the patient could live with the transplant.⁹⁸ However, if new organs could be printed in a matter of days from one's own tissues, new systems or guidelines may be required to regulate the use of these tissue or organ printers. Other ethical dilemmas raise questions about payment for these bioprinted tissues; will they be paid out of

94. Ting Zhang et al., *Mechanical Characterization of Bioprinted In Vitro Soft Tissue Models*, 5 BIOFABRICATION 1, 2, 6, 8 (2013).

95. de Vries, *supra* note 89, at 368.

96. Howard Wolinsky, *Printing Organs Cell-By-Cell: 3-D Printing Is Growing in Popularity, But How Should We Regulate the Application of this New Technology to Health Care?*, 15 EMBO REP. 836, 837 (2014).

97. *Id.* at 838.

98. UNITED NETWORK FOR ORGAN SHARING, TALKING ABOUT TRANSPLANTATION: WHAT EVERY PATIENT NEEDS TO KNOW 1, 7 (2013), available at <https://www.unos.org/docs/WEPNTK.pdf>.

pocket or will they be billed by insurance?⁹⁹ Will only people who can afford these tissues be able to print them?

G. Lifespan Extension and Advancement of Human Capability

As technological capability advances and bioprinted tissues and organs become available, questions will arise as to whether these tissues need to be primarily used only to replace diseased and injured tissue or to fight the negative consequences of aging. The possibility exists that this technology could be misused to extend human lifespan.¹⁰⁰ In professional sports, there are potential risks of the use of bioprinted tissues for performance enhancement if used for repair or replacement of injured tissues or to gain unnatural advancement of human capabilities.¹⁰¹ In the cosmetic industry, bioprinting may enable plastic surgeons to print body parts or tissues that are more aesthetically pleasing to replace undesirable parts or diseased tissues.

H. Conflicts of Interest of the Experts

The development, testing, and marketing of tissue-engineered or bioprinted organs may involve a select group of scientific experts in the field, so it is essential to address beforehand any financial, professional, or personal conflicts of interest that may arise so that the patient's best interest is always the highest priority. The people involved in clinical trials or treatments using bioprinted organs should provide full disclosure about financial and intellectual property interests.¹⁰² Also, to ensure full transparency about the development, testing, and clinical use of these products, details of the techniques used, cell sources, and costs should be fully disclosed or made available on request so that unbiased evaluations of the product can be conducted.

99. Wolinsky, *supra* note 96, at 838.

100. *Id.*

101. *Id.*

102. Justin Lowenthal et al., *Specimen Collection for Induced Pluripotent Stem Cell Research: Harmonizing the Approach to Informed Consent*, 1 STEM CELLS TRANSLATIONAL MED. 409, 414 (2012).

V. CURRENT FDA PRODUCT CATEGORY DESIGNATIONS

Organ bioprinting is a relatively new area of 3-D printing; hence, the FDA does not have one product category for bioprinted products.¹⁰³ Tissue engineered organs are typically combination products and may include pharmaceuticals, medical devices, and biologics, while their use involves the application of surgical procedures.¹⁰⁴

New surgical procedures are not regulated by the FDA and can be used on an ‘as needed’ basis at the discretion of the surgeon performing the operation; these organ transplant procedures are regulated by Health and Human Services and not the FDA. But surgically-implanted, engineered organs or tissues, depending on their composition, fall under the purview of the FDA either as devices or biologics. New medical devices, on the other hand, are federally regulated, which means that a device must be tested in clinical trials before a surgeon is allowed to use it in clinical practice.¹⁰⁵

Due to their composition, typically most bioprinted products are initially classified and regulated as either devices or biologics. Currently, products that use stem cells or are derived from stem cells are treated by the FDA as somatic cellular therapies and are regulated as ‘biologics’ under Section 351 of the Public Health Act.¹⁰⁶ As cellular therapies, they are also subject to FDA guidelines for the manufacture of human cells, tissues, and cellular and tissue-based products found in part 1271 of the same act.¹⁰⁷ Part 1271 establishes the requirements for donor eligibility procedures not found in the current good manufacturing practices guidelines of parts 210 and 211.¹⁰⁸ These guidelines regulate the way stem cells are isolated, handled, and labeled. Bioprinted tissues typically used in research do not require FDA approval during animal and *in vitro* testing because they are not

103. Wolinsky, *supra* note 96, at 838.

104. Faulkner et al., *supra* note 80, at 2277.

105. Taylor et al., *supra* note 87, at 879.

106. 21 C.F.R. § 1271.10 (2014); *see also* Dina Gould Halme & David A. Kessler, *FDA Regulation of Stem-Cell-Based Therapies*, 355 NEW ENGLAND J. MED. 1730, 1730 (2006); Mary Ann Liebert, *Guidance for Human Somatic Cell Therapy and Gene Therapy*, 9 HUMAN GENE THERAPY 1513, 1514–15 (1998).

107. 21 C.F.R. § 1271.10.

108. Human Cells, Tissues, and Cellular and Tissue-Based Products, 21 C.F.R. §§1271.45 to 1271.90 (2014).

intended for use on humans. However, Title 21 of the Federal Code of Regulations defines certain restrictions with regard to shipping and disposal of these products.¹⁰⁹

VI. INTELLECTUAL PROPERTY

Intellectual property can protect all the steps involved in the bioprinting process, including the fusion of the different bioprinted layers to form the final tissue construct, the different CAD files and CAM software that control the bioprinting process, and the bioprinters themselves.¹¹⁰ Patents would cover the bioprinters, bioprinting materials, and fabrication and post-production maturation processes, while copyrights would protect the CAD-CAM files for scanning, manufacturing, and bioprinter control.¹¹¹ The United States Code permits patents on “any new and useful process, machine, manufacture or composition of matter.”¹¹² According to that definition, products of nature are not patent-permissible; however, variations of naturally occurring organisms may be patented. The validity of several patents granted by the United States Patent and Trademark Office over the last few years on work related to human genes and other naturally occurring phenomena is questionable. In the Supreme Court’s landmark decision *Association for Molecular Pathology vs. Myriad Genetics Inc.*¹¹³ the Court held that patents on isolated, naturally occurring DNA segments were not valid, and reasoned that the patented research work did not create or alter any of the genetic information encoded in the genes.¹¹⁴ However, patents on complementary DNA, which is synthetically created DNA, are valid because complementary DNA are not natural products of nature.¹¹⁵ There is an analogous argument that bioprinted organs are not products of nature, but artificially created, and hence should be patent-eligible.¹¹⁶ Applications of 3-D printing have been

109. *Id.* §§ 1271.60(c), 1271.265(d), 1271.440.

110. John F. Hornick, *3D Printing and the Future (or Demise) of Intellectual Property*, 1 3D PRINTING 34, 34 (2014).

111. *Id.*

112. Inventions Patentable, 35 U.S.C. § 101 (2012).

113. *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 113 S. Ct. 2107 (2013).

114. *Id.* at 2111.

115. *Id.*

116. *See generally id.* at 2110.

subject to patent, industrial design, copyright, and trademark law for decades; however, there is very limited experience regarding how these laws would be applied to bioprinting when used to manufacture items for personal use, nonprofit distribution, or commercial sale.¹¹⁷ Based on the above arguments, patents for human organs will not be valid, but it is not clear whether an artificially printed organ would be patent-eligible.¹¹⁸ According to Gartner Inc., a market research group, 3-D printing will result in the annual loss of at least \$100 billion globally due to intellectual property theft.¹¹⁹ Although currently intellectual property theft is not an issue because bioprinting involves more complexity than normal 3-D printing and because the file formats used are typically customized to the printers employed, it could soon become an area of concern¹²⁰ if not appropriately regulated.

VII. ORGAN BIOPRINTING – CHALLENGES

A variety of technical challenges need to be overcome in order to ensure successful bioprinting of organs. The most important criterion is maintenance of cell viability in the bioprinted organs, since they will be exposed to different conditions, such as temperatures or microenvironments, during the various printing and processing steps.¹²¹ The ability to print a functional vasculature will enable the establishment of blood supply in these organs and thereby maintenance of cell viability.¹²² Another important aspect would be recapitulation of the exact 3-D microstructure of these organs, which would facilitate interaction between the different types of cells in these organs and allow for complete functionality of the respective organ.¹²³ Overall, the damage to cells during printing should be limited to the order of five to ten percent of the entire cells used in the bioprinted

117. Hoy, *supra* note 38, at 97.

118. *Id.* at 96–97.

119. Press Release, Gartner, Inc., *Gartner Says Uses of 3D Printing Will Ignite Major Debate on Ethics and Regulation* (Jan. 29, 2014), <http://www.gartner.com/newsroom/id/2658315>.

120. Hoy, *supra* note 38, at 97.

121. See Atala & Murphy, *supra* note 9, at 775–76.

122. Ozbolat & Yu, *supra* note 3, at 695.

123. *Id.* at 694.

construct in order for the construct to be viable.¹²⁴ It is especially challenging for cell types such as neurons, hepatocytes, and pancreatic cells to survive these extreme conditions.¹²⁵

Currently, vascularity, or establishment of a stable blood supply in the bioprinted organ, is the most challenging technical hurdle in the field of bioprinting.¹²⁶ Proof-of-concept studies using bioprinting have been successful, but the organs that have been produced are relatively simple—often avascular, aneural, alymphatic, thin, or hollow—and are nourished by the diffusion from host vasculature.¹²⁷ In order to engineer complex 3-D solid organs whose thickness is greater than the oxygen diffusion limit of 150 to 200 micrometers, precise multicellular structures with vascular networks that supply oxygen and other nutrients will need to be developed.¹²⁸ For successful utilization of bioengineered human tissues and organs for implants, they must have a built-in vascular architecture consisting of a complex network of highly branched blood vessels.¹²⁹ Scientists are currently testing a number of state-of-the-art approaches to address this challenge.

Another challenge is developing the ability to recapitulate the native tissue architecture in the bioprinted organ.¹³⁰ Each tissue and organ system contains multiple types of cells, arranged in a very intricate three-dimensional network, coordinating and serving a complex set of functions.¹³¹ It is relatively easy to generate digital models for simple tissues or organs such as cartilage, bladder, or skin.¹³² However, the structural complexity of organs such as the brain, heart, and kidney makes it extremely challenging to recapitulate the exact 3-D biological details of these organs.¹³³ Also, maintaining and establishing the interactions

124. Shannon Fischer, *The Body Printed: How 3-D Printing Could Change the Face of Modern Medicine and Why That Future Is Still So Far Away*, 4 IEEE PULSE 27, 30 (2013).

125. See generally Atala & Murphy, *supra* note 9.

126. Ozbolat & Yu, *supra* note 3, at 695.

127. Carl Schubert et al., *Innovations in 3D Printing: A 3D Overview from Optics to Organs*, 98 BR. J. OPHTHALMOL. 149, 160 (2014); Gross et al., *supra* note 36, at 3246–47; Xiaofeng Cui et al., *Thermal Inkjet Printing in Tissue Engineering and Regenerative Medicine*, 6 RECENT PAT. DRUG DELIV. & FORMUL. 149, 149 (2012).

128. Shubert et al., *supra* note 127, at 160–61.

129. Taylor et al., *supra* note 87, at 879–81.

130. Atala & Murphy, *supra* note 9, at 775; Schubert et al., *supra* note 127, at 160–61.

131. Cui et al., *supra* note 127, at 2.

132. Fischer, *supra* note 124, at 28.

133. *Id.* at 28, 30–31.

between the different cell types in the organ will be challenging. Cell to cell interactions play a major role in the biological function of tissues and organ systems. Once the cells have been printed, given the optimum growth conditions, the cells should self-organize into a network to form a functional and usable bioactive construct.¹³⁴ Cells within thick, vascular tissues, such as the heart, brain, and kidney, require a vast variety of growth factors and signaling factors to help them integrate into a functional network after printing.¹³⁵ This final step of establishing interacting networks among the cells will also depend on the overall cell viability, vascularity, and 3-D structure of the printed construct.

VIII. CONCLUSION

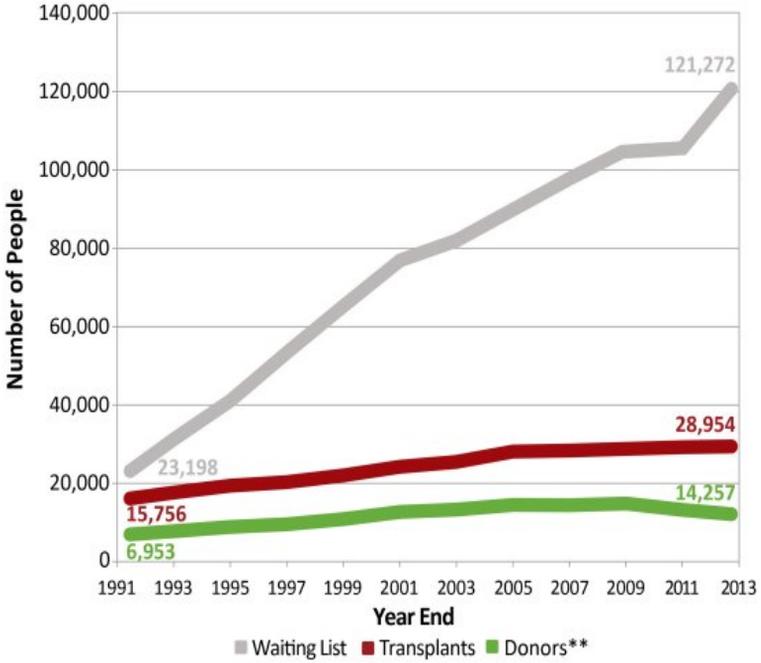
Organ bioprinting has emerged in the past few years riding on technological advancements in stem cell technology, cell and molecular biology, biomechanical engineering, and printing and software technologies. Bioprinting is developing as an enabling technology that will enhance our abilities in tissue engineering and regenerative medicine in terms of providing more precision, reproducibility, and control on developing heterogeneous complicated microstructures that will be required for mass production of tissue engineered organs. Public policies need to be framed and enacted to ensure that bioprinting technology is ethically used and developed for the wider wellbeing of humanity.

134. Schubert et al., *supra* note 127, at 160.

135. Gross et al., *supra* note 36, at 3247.

IX. FIGURES

A. *Figure 1: Recent data from the Organ Procurement and Transplant Network is indicative of the widening gap in supply and demand of donor organs.*



B. Figure 2: Scheme shows the typical tissue engineering approach followed for organ fabrication. Modified and adapted from Ref. 47.

