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Title: 3D Printing in Healthcare: An Engineering and Technology Management Perspective

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1. Abstract

3D Printing is a radical innovation that is enabling us to create personalized objects at low cost and quickly. Similar to Amazon's success in the revolutionizing the retailing industry with Ecommerce, 3D printing technology is showing the promise of turning healthcare on its heel with its capacity of rapid prototyping and personalizing the solution to the patient. This gives us an opportunity to study this innovation using technology management principles and tools. We explored the technology using engineering, technology forecast and motivating factors (Stengths, Weaknesses, Opportunities and Threats (SWOT)) models. We also conducted a market analysis to assess the expected economic return. The study highlighted the engineering challenge in developing the right biological materials and the appropriate 3D printing manufacturing processes. A time-based trend analysis of Bibliometrics in this technology segment drew us to the conclusion that this technology is straddling the innovator and the early adopter phases of the Technology Adoption Life Cycle (TALC). On the policy side, the motivating factors study highlighted the legal, ethical and regulatory challenges. But, the motivating factors review also highlighted the expansive benefits, both profit-based and humanitarian, of this technology. The research put together, showed that this disruptive technology will be a game-changer in the future of healthcare.

Keywords: 3D Printing, Healthcare, Technology Management, Technology Policy

2. Introduction

Rapid advances in technologies to manufacture at the nanoscale are applied to many objects of today ranging from fuel cells to nanoparticle based skin creams, e.g. Nano Gold Energizing face cream from Chantecaille Beauté. We also have unprecedented abilities to draw, define and visualize data at sub-molecular levels using Computer Aided Design (CAD) tools. We can combine our visualization capabilities and the knowledge of chemicals and their interactions with this nanotechnology manufacturing methods to grow devices using an additive manufacturing process, which is commonly referred to as 3D printing. Applications for 3D printing are enormous and wide as recognized by several leading technology exponents, such as a January 2015 report from the Scientific Foresight (STOA) Unit of the European Parliament [1]. This research paper is specifically directed to one of the revolutionizing applications of this technology, in human well-being advancement. There has been enthusiastic response from the healthcare industry in adapting 3D printing technology for medical education, faster and more reliable drug development, faster/cheaper cosmetic testing, prosthetic, reconstructive and organ regenerative purposes. The key drivers for this interest are the customization or personalization, reduced time and costs of 3d bio-printing over traditional approaches.

With revenues of $ 56.63 billion in the US [2], the cosmetic industry is a major beneficiary of 3d printing through quicker and more thorough testing using bioprinted tissues.

In a December 2014 Journal of American Medical Association article, some of the applications of 3D printing technology and their importance to the healthcare industry have been explored by Drs. Michalski and Ross [3]. The United States Food and Drug Administration (FDA) conducted a public workshop in October 2014 on Additive Manufacturing of Medical Devices indicating the real presence and feasibility of the technology. The FDA granted 510(k) clearance for two 3D printed products from Oxford Performance Materials, the OsteoFab® Patient-Specific Cranial Device and the OsteoFab® Patient Specific Facial Device. The former was the first 3D printed polymeric implant and it was approved in

February 2013. The application of 3D printed models for pre-operative planning for the surgeon and patient education is depicted in media report of the role of 3D printed model the defective heart of a two-year in pre-operative planning [4].

According to data from the US Department of Health and Human Services [5], the disparity between organ donors and transplants completed continues to grow year over year as shown in Figure 1. According to a New York Times Investigative report by Kevin Sack [6], global trafficking of organ trade is a current threat. It has influenced the attendees of a worldwide conference of transplant practitioners to put together a manifesto called the Declaration of Istanbul [7] which was first published in 2008 in the Lancet. It has since been published in several other medical journals and the declaration has been endorsed and adopted by more than 130 transplant organizations worldwide. 3D printing technology presents a novel method and opportunity to close this gap through a humane, legal and ethical approach. This vision is turning into reality as depicted by the first commercial 3D printer, the NovoGen MMX Bioprinter™ [8], developed jointly by the companies Organovo and Invetech, which can print human tissues.

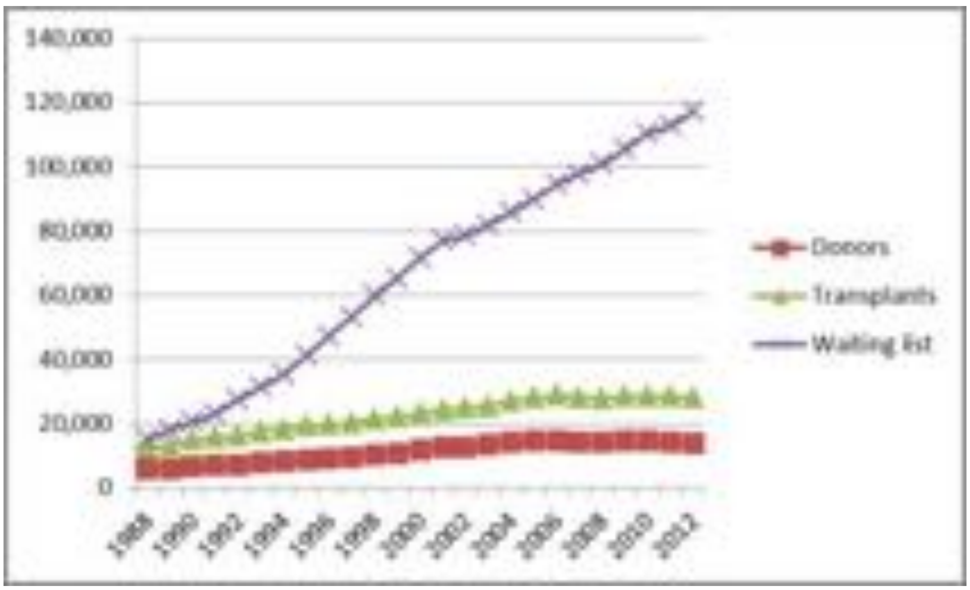


Figure 1. Gap between organ donors and waiting list [5]

The specialized process of 3D bioprinting can be simply described as a three step process below and is shown in Figure 2.

1. The cells, which will become the biological ink, are first harvested from a possible variety of sources and then grown in a culture
2. A hydrogel which are based upon cross linked polymers with hydrophilic properties become the smart material or the binding agent for the cells
3. The cells (bioink) and the hydrogel (binding agent) are then combined and dispensed layer by layer (additive manufacturing) and developed in a growing container under varying environmental and sit time conditions to develop into the final desired structure

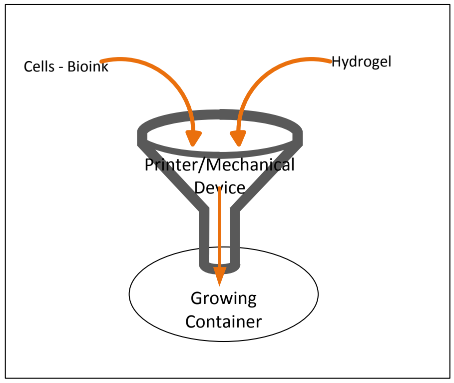


Figure 2. 3D Bioprinting Process

3. Literature Review

The focus on cost in manufacturing and advances in digitization, has led to the definition of a new manufacturing model, termed Additive Manufacturing. This model promises to increase precision as well as cut waste in terms of time and costs of the traditional approach, termed Subtractive Manufacturing. In a Special Report in *The Economist*, Additive Manufacturing is hailed as the Third Industrial revolution, following the First Industrial revolution in the late 18th century with the mechanization of textile mills in Great Britain and the Second Industrial revolution of the early 20th century in America with the concept of the assembly line leading to the era of mass production [9]. 3D Systems, Inc. is one of the oldest companies in the commercialization of 3D printers, having invented the 3D printing process with Stereolithography (SLA) as well as pioneered several other new 3D printing methods such as Selective Laser Sintering (SLS) and Virtual Surgical Planning (VSP). The precision and material options offered by 3D printing technology have been used in dentistry and hearing aids for a while now and is being expanded into medical applications internal to the body. Internal application of 3D printed devices can be of two types, implants that are reconstructive in nature, e.g. orthopedics, or implants that are regenerative in nature, e.g. organ transplants.

Given that reconstructive applications are less complex than organ implants, several technology studies have been conducted on the materials, processes and challenges for reconstructive applications of 3D printing. An integrated approach using CAD and 3D printing processes for auricular and nasal reconstruction is described by D Zopf *et al* [10]. The challenges with printing at clinically relevant dimensions that promote bone strength issues is described by N E Fedorovich *et al* [11]. The OsteoFab® Patient Specific Facial Device printed by Oxford Performance materials is shown in Figure 3.

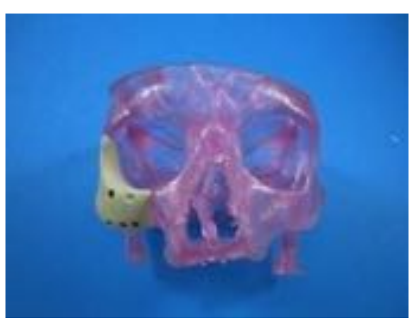


Figure 3. OsteoFab® Patient Specific Facial Device (courtesy: Oxford Performance Materials) [12]

An in-depth technology focused analysis identified the need for advances in cell technology, manufacturing technology and technologies for integrating (thereby preventing rejection) into the body as the key challenges [13] for bioprinting for organs. Organs are printed using cells as the bioink and hydrogels. Cell culture involves taking a few living cells and then multiplying them under a controlled laboratory environment using techniques that will promote their multiplication. How these cells aggregate are critical to the final intended organ and they have found that between two techniques Hanging Drop (HD) and Conical Tube (CT), smaller HD aggregates are a better choice for the bioink [14]. Hydrogels were discovered in 1960s by Wichterle and Lim [15] and first successfully used in the manufacture of contact lenses. Hydrogels are three-dimensional polymer networks that have hydrophilic properties, i.e. they can retain water in specific states. They have been used for controlled drug delivery as well as tissue engineering [16]. A conceptual representation of organ bioprinting is shown in Figure 4 [17].

Figure 4. Conceptual representation of bioprinting an organ (courtesy: Christopher Barnatt) [17]

We are enhancing our knowledge and capabilities of using smart materials. By embedding minimally invasive three-dimensional macroporous nanoelectronic networks into host materials [18] during the 3D bioprinting process that could communicative with external networks, we can monitor the patient. However, there are several considerations, e.g. complex biological interactions, and approaches, e.g. preclinical test beds that one must take in this development of smart materials [19]. An example of smart embedded 3D printed device used in medical application was a smart bandage that can monitor for wound oxygenation [20].

A more detailed explanation of the 3D Bioprinting process and its applications in medicine is described in Appendix A [21]. The major companies in this industry segment include: 3D Systems, Arcam, Concept Laser, DWS, EnvisionTEC, EOS, Innovation MediTech, Materialise, Optomec, Rapid Shape, Renishaw, SLM Solutions, Solidscape and Stratasys Ltd. [22].

The literature information gathered indicates that the 3D printing technology in healthcare within the context of innovation process [23], as shown in Figure 5, is in the "research and invent" space with some promising application into the market once the technology is developed.

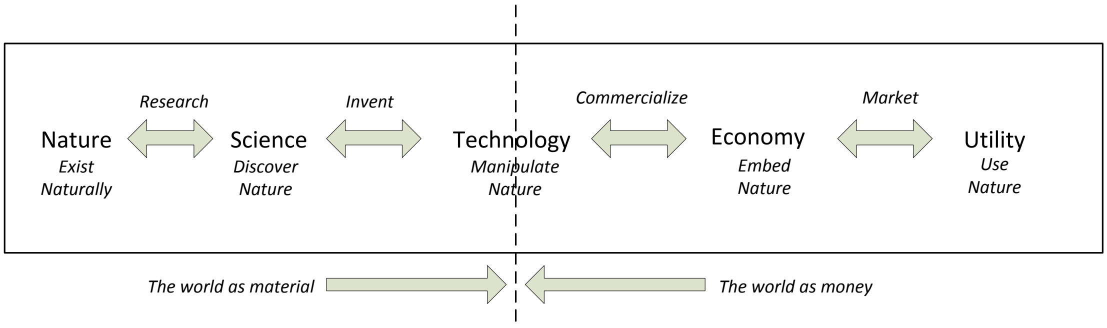


Figure 5. Innovation Process [23]

4. Methodology

Given that the technology is in the research and invention space of the innovation process, the major focus from an engineering and technology management perspective would be risk management. Risk can be analyzed along technology, market, future and policy vectors. Accordingly the study was divided into four sections:

1. A review of the various 3D printing technology processes to understand its applicability to healthcare needs
2. Market analysis to understand the potential for economic return
3. Using current research publication metrics and adjacent older technology research publication metrics to predict future research trend. For the adjacent older technology Electric Vehicles was chosen as it is a field older than 3d printing in health with a similar application model in that electric vehicles use an alternative energy source
4. Categorizing and studying various factors and policies that will provide us with a SWOT analysis that will help develop additional risk mitigation tactics during technology development

All the information was gathered from a variety of literary sources, ranging across articles, reports, journals and internet websites.

5. Data Collection and Results Analysis

5.1 Technology Review

Bioprinting is a technology that uses specialized printers, referred to as bioprinters, to output cells from a printer head that moves left and right, back and forth, and up and down, in order to place the cells exactly where required. Over a period of several hours, this permits an organic object to be built up in a great many very thin layers. In addition to outputting cells, most bioprinters also output a dissolvable gel to support and protect cells during printing [17]. Living tissues and organs are composed of many cell types. They are arranged in a very specific order in three-dimensional space. In order to ensure engineered tissues and organs to function properly, it is essential to maintain the same structure that original body parts have.

The building block for an organ is cell since organs are made of tissues, and tissues are made of cells. In order to print an organ, scientists must be able to deposit cells that are specific to the organ they hope to build. For example, to print a liver, scientists would start with hepatocytes which are the essential cells of a liver. These cells form a special material known as bioink, which is placed in the reservoir of the printer and then extruded through the print head. As the cells accumulate on the platform and become embedded in the microgel, they assume a three-dimensional shape that resembles a human organ [24].

Bio-printing technology is still under development and not ready for actually replacing human organs. However, 3D printing technologies in medical industry have made a huge leap especially in the field of prosthetics, prototype for pre-operation planning, medical instrument and apparatus. There are four main technologies in 3D printing that have been influencing the medical industry: selective laser sintering, stereolithography, fused deposition modeling, and polyjet.

5.1.1 Selective Laser Sintering

Selective Laser Sintering (SLS) is an additive rapid 3D Printing process that builds three dimensional parts by using a laser to selectively sinter (heat and fuse) a powdered material [25]. The primary material for SLS is nylon which offers flexible parts that are good for field testing. The printing process begins with a 3D CAD file which is mathematically sliced into 2D cross-sections. The SLS prototype or part is built a layer at a time until completed. The SLS 3D printing process has many advantages. Since this technology is compatible with 3D CAD, it is widely used as in the beginning of the design concept. Moreover, the high level of accuracy, relatively cheap feedstock, and high temperatures achievable with SLS printing make it an incredibly useful technology with a broad range of applications ranging from architectural models to control surfaces of aircraft and surgical tools [26]. However, the lead time for SLS is relatively longer compared to other manufacturing process especially with larger parts. Also, the cost for SLS is relatively high. An SLS system developed by C Shuai *et al* and used for medical application is shown in Figure 6 [27].

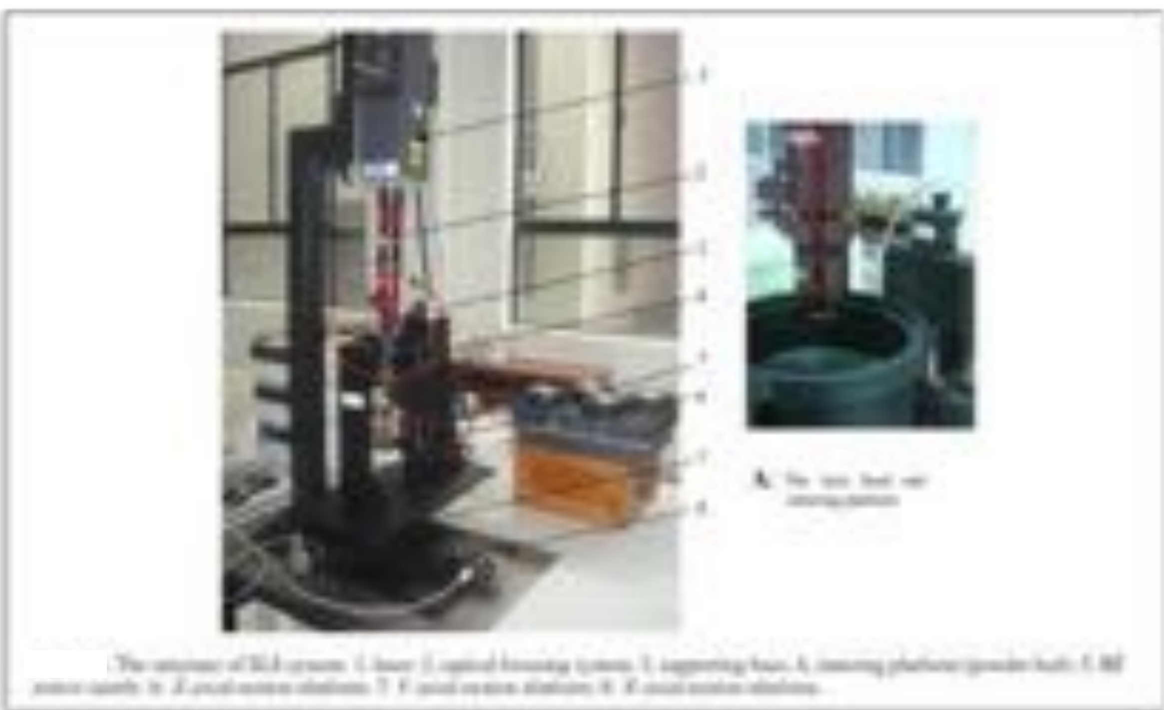


Figure 6. An SLS machine [27]

5.1.2 Stereo Lithography

Stereolithography (SLA) is an additive process which employs a vat of liquid ultraviolet curable photopolymer "resin" and an ultraviolet laser to build parts' layers one at a time. For each layer, the laser beam traces a cross-section of the part pattern on the surface of the liquid resin. Exposure to the ultraviolet laser light cures and solidifies the pattern traced on the resin and joins it to the layer below. SLA has many advantages. Parts can be made very shortly. A design can be created through the SLA process in less than two days. This is great for demonstration purposes because it allows for quick turnaround if a design needs to be tuned or modified. SLA is able to create smoother surfaces than most other rapid prototyping methods. Smooth surface means a high level of design detail and designs will be ultra-accurate. Not only are the surfaces of the products nice to look at, but they are also high quality surfaces. Moreover, SLA is the primary method that is used when printing custom medical materials. This is possible because SLA is able to produce items that are water resistant. SLA also offers a variety of different finish and material options which mean you can create a prototype that is very close to the finished product [28]. The only downside of SLA is high cost and long lead time. A Projection Stereo Lithography (PSL) system designed by R Gauvin *et al* and used for medical application is shown in Figure 7 [29].

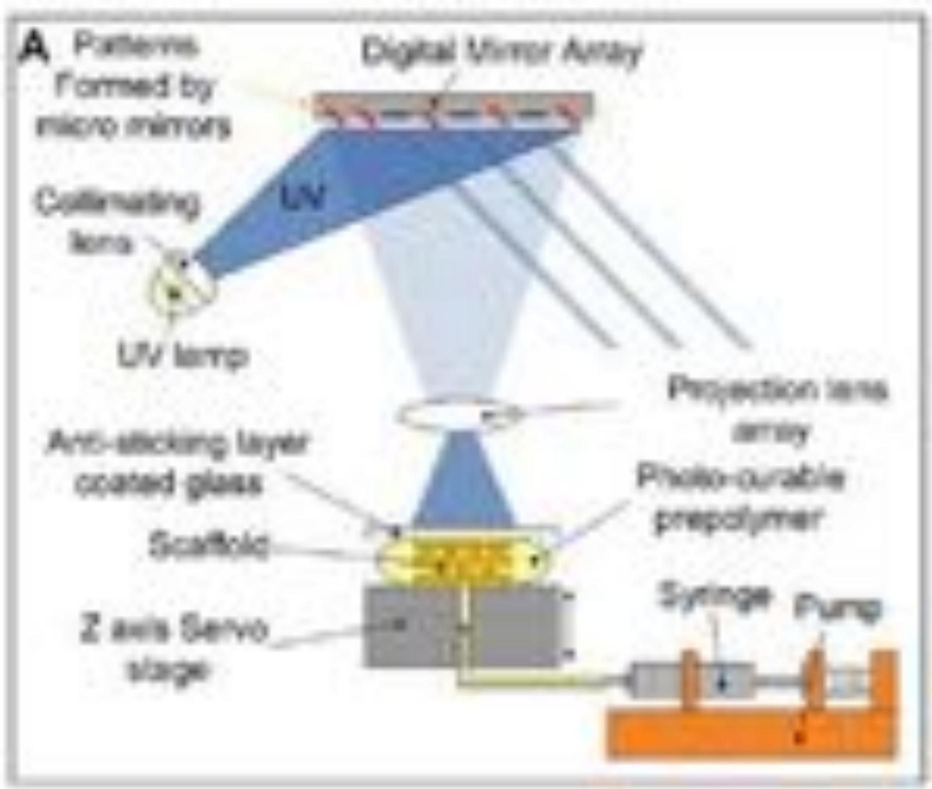


Figure 7. A Projection Stereolithography system [29]

5.1.3 Fused Deposition Modeling

Fused deposition modeling (FDM) is an additive manufacturing process that extrudes thermoplastics from a heated nozzle to produce 3D objects. It is the most common used process for modeling, prototyping, and production applications. FDM has many advantages. First is speed. The process can produce parts within minutes to a few hours. Second, it is also relatively cheap and affordable. It only cost a few dollars to produce a small part. Third, it is easy to use since the entire process from design to manufacturing is controlled by computer. Fourth, there is very limited design restriction since FDM is fully compatible with CAD application. Fifth, FDM has the ability of automatic scaling. The process accurately scales part to fit inside machine production space. Disadvantages of FDM include lower accuracy compared to other technology and the surface finish of products can be rough. An FDM system designed by I Zein *et al* and used in healthcare application is shown in Figure 8 [30].

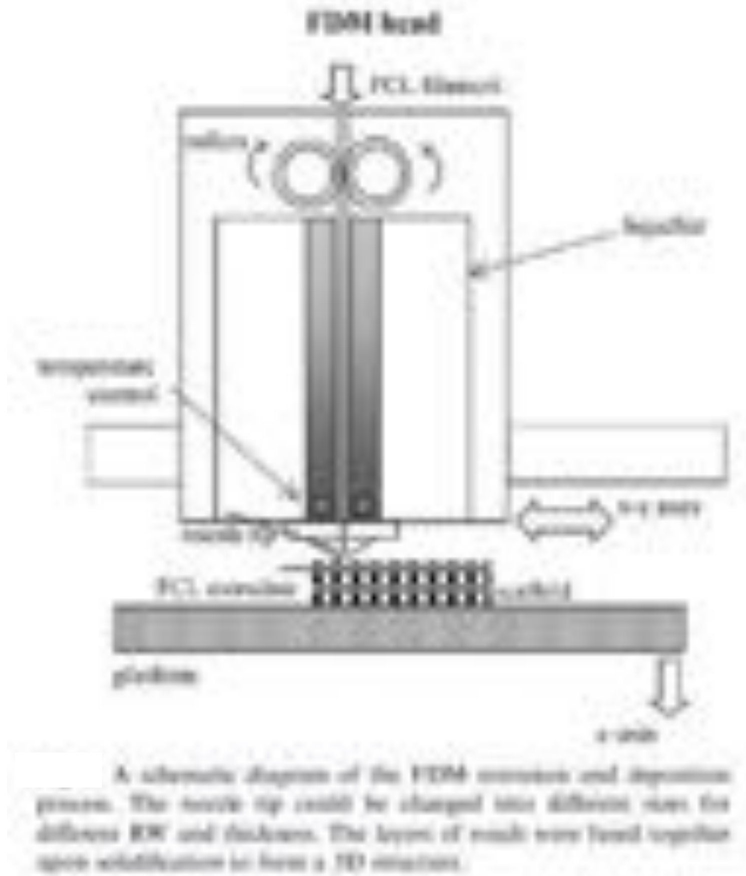


Figure 8. An FDM System [30]

5.1.4 PolyJet

PolyJet 3D printing is similar to inkjet document printing, but instead of jetting drops of ink onto paper, PolyJet 3D Printers jet layers of liquid photopolymer onto a build tray and instantly cure them with UV light. The layers build up to create a precise 3D model or prototype. Along with the selected model materials, the 3D printer also jets a gel-like support material specially designed to uphold overhangs and complicated geometries. It is easily removed by hand or water [31]. PolyJet 3D Printing technology offers many advantages for rapid tooling and prototyping, and even end-use parts including astonishingly fine detail, smooth surfaces, speed and precision. PolyJet 3D process creates smooth, detailed prototypes that convey final-product aesthetics. It also produces short-run manufacturing tools, jigs and assembly fixtures. PolyJet 3D can produce complex shapes, intricate details and smooth surfaces. Moreover, the process has the ability to incorporate color and diverse material properties into one model with the greatest material versatility available [32]. However, PolyJet 3D is one of the most expensive process, so it is preferred to use for late-state development prototyping. The process also requires support material which can drive the cost even higher. A sample PolyJet Process is described in shown in Figure 9 [33].

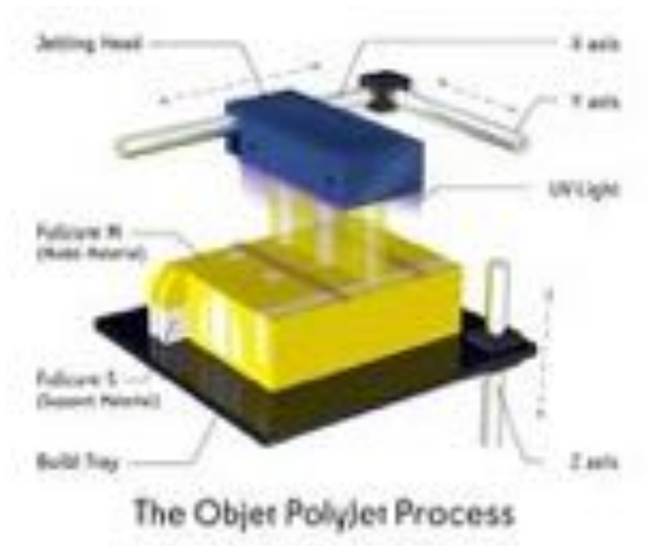


Figure 9. A PolyJet Process [33]

5.2 Market Analysis

In order to understand the 3D bioprinting market such as how it performed in the past, what achievements and results it has gained recently, and how it would be in the next decade, we decided to do literary and market research. The important facts are summarized below.

For 3D printer market in general, we found that the 3D Printer Manufacturing industry earned 35.5% in the whole product and service segmentation in 2015 (See Appendix B). Over the five years to 2015, revenue is expected to grow at an average annual rate of 22.4% to total $1.7 billion. In 2015, revenue is expected to grow an additional 15.8% [34].

In medical device manufacturing, 3D printers are progressively being used to generate modified medical devices that more precisely imitate the human form. These products include hearing aids, orthopedic implants and dental implants; furthermore, upcoming applications such as 3D-printed organs and blood vessels are in development [34].

Over the next five years (2015-2020), industry demand and revenue are predicted to surge as 3D printers rise in popularity and draws more customers from a wide array of industries that could use 3D printing. In this period, IBISWorld projects that industry revenue will grow at an average annual rate of 12.3% to reach $3.1 billion [34]. Among the other application fields of 3D printing, bioprinting for healthcare considered occupied a big segmentation which is 20% of the whole 3D printing market (See Appendix C).

These are some facts related to the emerging of 3D bioprinting market [35]:

- It would take 1,690,912, 929, 600 hours to print a liver for every member of the human race using today's processes (See Appendix D)
- The number of people on waiting list for an organ transplant increases every year, yet the amount of donors and available organs remains at a low.
- USA: more than 114,300 (2012) people on the waiting list as candidates
- More than 73,000 active waiting list candidates
- In 2005, 1848 patients died waiting for a donated liver to become available (USA)
- 1700 adults and children have been medically approved for liver transplant and are waiting for donated livers to become available (January 2012)
- Drug industry problem:
    - Each year, the industry spends more than $50 billion (USA, 2012) on R&D and approximately 20 new drugs are approved by FDA
    - A new drug, on average cost $1.2 billion and takes 12 years to develop

These above facts could be considered as factors that would drive an increasing demand of 3D printers and medical devices, for bioprinted organs. For example, consider a case of kidney transplant which costs average $334,300 [36] for a person to get this treatment (See Appendix E). Moreover, even though a patient can afford the above cost, the risk that the patient's immunization system could reject the transplant kidney is also high.

For more than two decades (See Appendix F), tissue engineering with bioprinting has been consistently making forward strides and has the following notable achievements [37]:

- Artificial Bladder (2006) – USA [38]
    - World's first artificial bladders built by an 3D printing in a technology lab
    - First test of artificial bladder on dogs (1999)
    - 2006: Transplantation on 7 human patients
- Artificial Liver (2009) – USA (Wake Forest University School of Medicine)
    - Bio-engineering human liver (5.7g)
    - 3D printing of collagen skeleton
    - Application of human liver cells on skeleton matrix
    - Artificial liver is then placed in a bioreactor (nutrients and oxygen)
    - One week after: cell growth inside bioengineered organ with progressive formation of liver tissue as well as liver-associated functions

Below are some key players in 3D bioprinting market:

- Key vendors:
    - 3D Systems

  - EnvisionTEC
  - Organovo Holdings
  - Stratasys
- Prominent Vendors
  - 3D Biotek
  - Advanced Biomatrix
  - Bespoke Innovations
  - Digilab
  - regenHU
  - Nano3D Biosciences
- Key Regions
  - Americas
  - APAC
  - EMEA

After observations about the 3D Bioprinting market, the following business opportunities show major potential and have been developed [39]:

- Cancer tumor models
- Organ transplantation
- Design Model Making, the printer and the bio-material
- Pharmaceutical research
- Dentists: better implants and prosthetics based on patient tees layout and bone scans
- Organ secure storage and transportation for customer's organ.

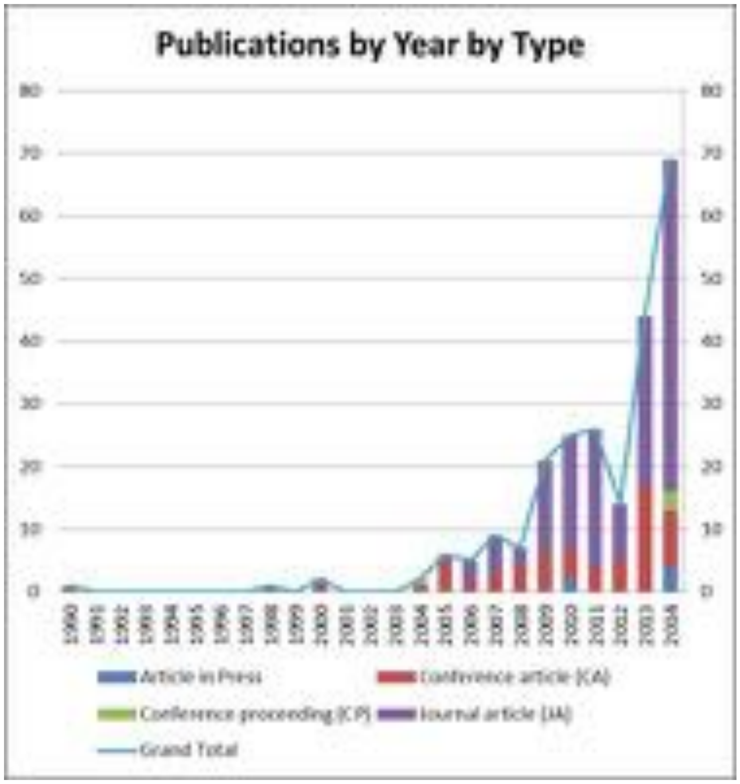
As one of key vendor of 3D bioprinter producers, Organovo was found with a listed stock price about $4.79 (See Appendix G). From a business perspective, there is one thing that could be considered is that what this price will be or is it a potential investment to invest in the next ten years.

In addition, some critical questions are raised such as: 1) Is the 3D Bioprinting market mature enough to invest currently, 2) How is the market will be in the next decade, 3) What is the technology of bioengineering and bioprinting will be in the next decade. To get more information to answer these questions or in order to define the potential market for 3D bioprinting, team had done some researches for Technology Forecast which will be described in the next section.

5.3 Technology Forecast

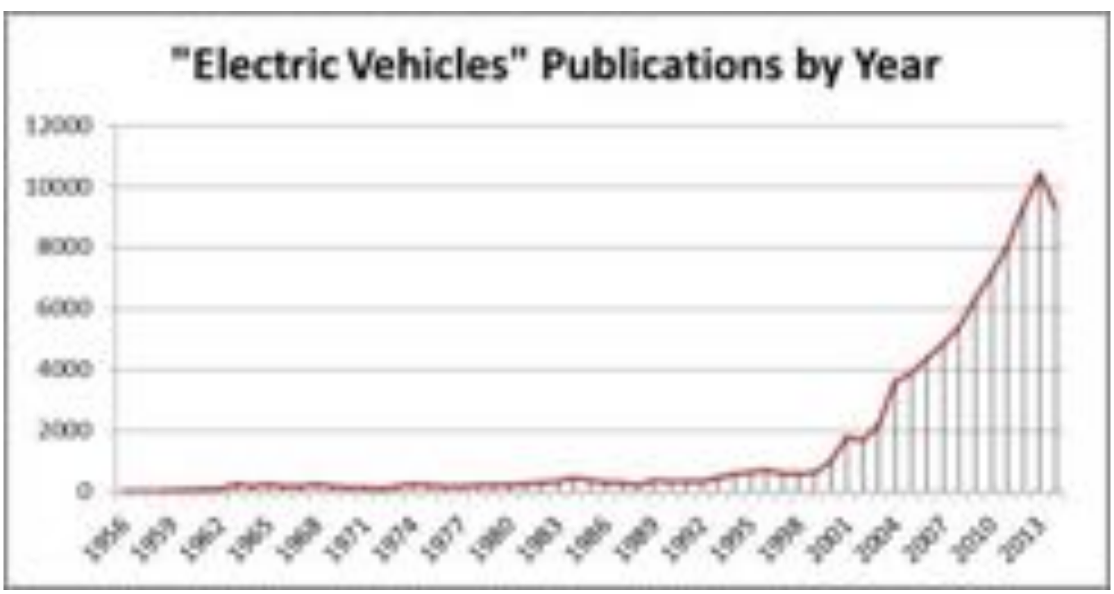
5.3.1 Bibliometrics Analysis

Using the Compendex and Science Citation Index databases as the data sources, a bibliometrics analysis was conducted. For publications related to 3d printing, the keyword chosen was "3d printing in medicine". The data from both the sources were combined and duplicates based upon titles were removed. The resulting data categorized by publication type is shown in Graph 1.



Graph 1. “3d printing in medicine” related publications by year and type

Graph 1 confirms that the research and exploration in this application of 3d printing in healthcare is a new area, with publications starting as recently as 1990. Publications on Electric Vehicles are shown in Graph 2.



Graph 2. “Electric Vehicles” related publications by year

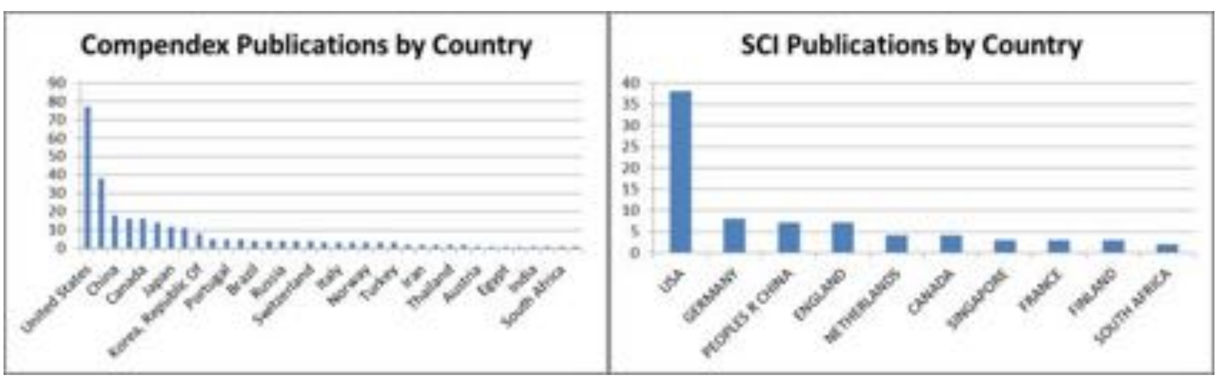
An overlay of both graphs are shown in Graph 3 for a shortened window of forty seven years.

Graph 3. Contrasting “3d printing in medicine” and “Electric Vehicles” publications

The trend in Graph 3 indicates that research in the area of 3d printing in medicine is slower than electric vehicles. Future study would be helpful to determine the key factors that are possibly preventing an increasing pace of research, possibly healthcare regulations and safety factors.

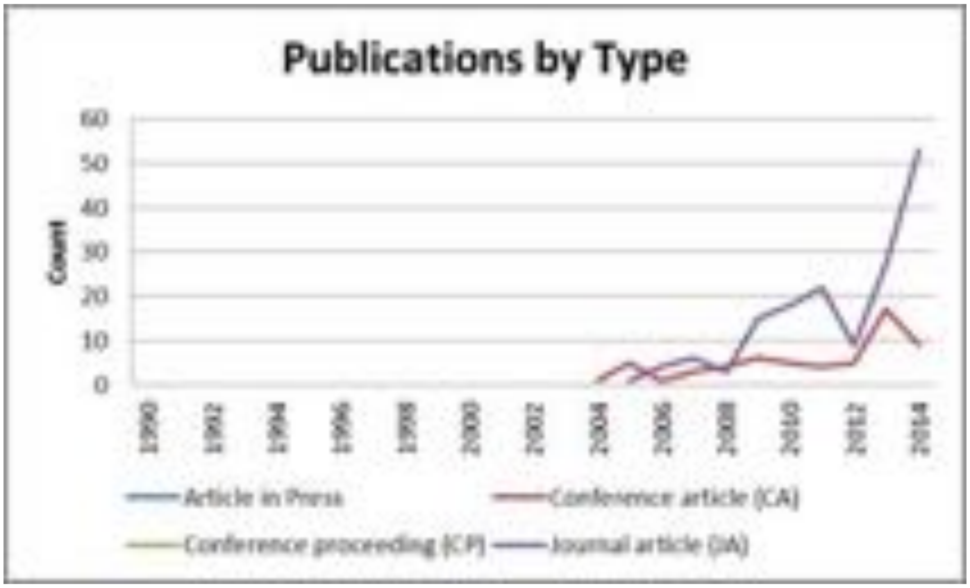
5.3.2 Additional Analysis

Analysis of publications by country as shown in Graph 4 shows the USA as the leading research location for this technology.



Graph 4. “3d printing in medicine” - Publications by Country

Another analysis of the data was to to look at the type of publicatoin as shown in Graph 5.



Graph 5. “3d printing in medicine” - Publications by Type

A possible deduction from the data in Graph 5 is that conference publications are still high compared to journal articles; this is another indicator of the relative maturity of the technogy in that conferences are more critical in the early stages of a technology and sparks the discussion and interest in moving the technology into laboratories for research.

5.4 Motivating Factors

The role of 3D printing is advancing at a very rapid rate and with, as of yet, unknown ramifications. With the development of new materials and manufacturing techniques, several questions regarding regulatory and ethical questions need to be understood. While these questions are posed, companies are quickly realizing the potential market and profitability of transitioning 3D printing into biomedical applications.

5.4.1 Materials and Manufacturing

With a variety of new bio-materials being developed such a collagen, chitosan and varying other synthetics, new advancements in the 3D manufacturing field are required to utilize these materials effectively. Multiple approaches have been developed including the generation of three dimensional scaffolds that can be seeded with these tissue materials often developed using embryotic stem cells. A bioreactor is then added to promote additional cell growth before the scaffold dissolves leaving only the biological tissue. Potential applications are abundant and include soft tissue opportunities, bone regeneration as well as base materials for drug testing and material interactions.

Understanding that tissues in the body are naturally compartmentalized with different cell types, the manufacturing techniques required to ensure stability must also vary. New biomedical polymers can be fabricated quickly and at the microscopic level. Techniques including photolithography, magnetic bioprinting, stereolithography, and direct cell extrusion are currently in development [40]. Some of the new materials being utilized consist of bioengineered substances and may actually prove to be stronger than the average naturally occurring bodily material. Substances such as Alginate [41], which is an anionic polymer, show strong biocompatibility, lower toxicity, and stronger structural abilities. Synthetic hydrogels are also becoming common place. With such variance in both material development and manufacturing process needs, the 3D printing industry is expanding pulling in development companies not previously involved.

5.4.2 Regulatory

From a regulatory perspective, the industry in general needs to catch up with the technology. Current 3D printing regulatory standards have not adapted to include specialized application were biological process are involved. Matthew Di Prima, a material scientist with the FDA, says "We are regulating 3-D printed devices the exact same way we regulate non-3-D printed devices" [42]. A few additional questions might be asked regarding the general manufacturing process but monitoring compliance is more related to simple device performance.

There are significant areas of concern when it comes to the use of 3D printing in the biomedical field. The general practice of 3D printing allows for complete customization. A broad variety of products sizes and adaptations combined with usage models inside the body present new challenges. For many, the perceived benefit far outpaces the risk involved so this poses an interesting question regarding how the Federal Drug Administration (FDA), and other regulatory agencies, will move to manage this industry. Normally for external devices, the FDA and EU are built to monitor standard sized devices whereas new devices will now be individually match for improved recovery. The general consensus is in the future most medical devices will be truly personalized to fit an individualized anatomy.

The idea of quick and customizable prototyping also raises an additional safety concern. With this capability becoming widely utilized across a vast range of products including guns, toys, prosthetics, etc., a developed market for surgically insertable products may be inevitable. Pete Basilier, with Gartner Inc., has stated "3D bioprinting facilities with the ability to print human organs and tissue will advance far faster than general understanding and acceptance of the ramifications of this technology" [43]. With medical costs for procedures such as joint or organ replacements being prohibitively high, the opportunity for unregulated back alley procedures seems likely. Already, organizations such as Doctors Against Forced Organ Harvesting are petitioning the United Nations for investigations into illegally obtained organs for transplant [44] [45]. Although the validity of these claims is discussion for a different paper, with the expected cost reduction in futuristic 3D printed organs, it seems rational to assume unregulated entities could become involved establishing a black market for implantable 3D printed devices.

The FDA has previously long established a classification with general guidelines for personalized medicine. Some early example of items to be classified as such include blood compatibility testing (1907) and the antimalarial drug Primaquine as it was discovered to be a deficiency in the metabolic enzyme glucose-6-phosphate dehydrogenase (G6PD) [46]. Additional later examples include developed enzymes that interact differently amongst patients. The concern, however, relates to the need for a clear definition for personalized medicine that can be adapted to include new 3D printing applications. Even according to the FDA, the proposed definitions vary significantly [47]:

- "Providing the right treatment to the right patient, at the right dose at the right time" – European Union
- "the tailoring of medical treatment to the individual characteristics of each patient" – President's Council of Advisors on Science and Technology
- "A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease" = National Cancer Institute, NIH

- "Health care that is informed by each person's unique clinical, genetic, and environmental information" – American Medical Association

To this end, within the FDA, the Office of Special medical Programs (OSMP) has initiated public workshops (started October 2014) to evaluate the challenges of regulating medical devices created through the use of 3D printing processes (also classified as additive manufacturing). While not yet mainstream, regulators clearly comprehend the trend of the industry and expect to see significant growth in the coming years. Submissions for device approvals including cranial implants and facial reconstruction have already been submitted for the OsteoFab® (3D printing device) made by Oxford Performance Materials. With the General guidance provided that the device is "substantially equivalent" to another device that is already marketed, the FDA has granted appropriate clearance (510k). Many, however, argue that these approvals are based solely on the manufacturing process and not on the end product regarding long term safety and effectiveness usually validated in the form of clinical trials. Continued ongoing debate is expected both within the FDA and also abroad as the European Union also takes up the discussion. Even smaller national regulatory agencies, such as the Tanzania Food and Drug Administration (TFDA) are now involved in the debate [48], establishing research budgets, and closely monitoring the USA and EU activities. Certainly pending decisions will have a great impact on the industry moving forward.

In all cases, the focal point of ongoing discussions will be to consider the overall benefits against the well-being of the patient. Expected guidelines and restrictions will focus on monitoring the rapid advances of the technology in an effort to encourage work in a positive and more predictable method. Collaboration between universities, government agencies and the scientific communities will be required to establish standards and develop clinical trials. The pipeline of products to market, including the advancement of drug and cosmetic testing enhanced by 3D printing, must be balanced between an ability to streamline opportunities, ensure process safety, and not cripple the advancement of science and technology.

5.4.3 Ethics

Related to the regulations requirements that are needed, a separate question is raised associated with ethical practices. The idea of 3D printing evolving to create new joint materials, skin patches, and even organ transplants seems to be taking a positive path in the right direction. However, consider this, the cells that are transplanted onto these 3D frameworks generally consists of embryotic stem cells. From a moral perspective, stem cell research has been an area of disagreement for a considerable amount of time correlating to religion and the definition of life. Certainly the manufacturing of new organs will spark additional debates.

Add to this the general materials being used in the 3D printing process. Titanium has been considered a very biofriendly material for joint replacement for a reasonable period of time. Titanium itself is stronger and more durable than organic bone. Add in synthetic ligaments and newly developed hydrogels and the potential for an improved end product exists. The future implications are that significant pieces of the human body could be replaced with feasible materials that are stronger, show acceptable biocompatibility, and reflect low toxicity levels for longer durations. Could we be looking at the beginnings of a potentially enhanced human? Lots of ethical questions are debated regarding the advancement of medicine and should we play God with our own bodies. With the potential opportunity that advanced 3D printing brings, this raises the debate around plastic surgery to a whole new level. Would athletes undergo optional surgery to enhance their physical characteristics?

5.4.4 Economics

It is perceived that the success rate of 3D printing, especially in emerging regions, will continue for several main reasons. We discussed the potential for increased access, the need for regulation and the ethical implications. Another considerable driving force relates to simple economics. Companies are willing to invest in the industry, both those that are already involved as well as new players, because the Return on Investment (ROI) is generally projected to be good. With a simplified supply chain, an increasing aged and growing population, and continued reduction in material and manufacturing costs, it simply makes business sense.

Cost projections associated with biomedical practices will continue to decrease based on several factors. An expected increase in demand combined with the increase in the number of competitors should drive overall material and research costs down. Additionally, with the expected increase in accessibility to 3D printers , along with the trend of highly customized solutions, companies won't be required to maintain inventories and associated risks. Finally, because of the customized technologies and application opportunities, the expected overall cost of critical care will be reduced [49].

With the ability of doctors to simulate operations using 3D models, the duration of medical procedures should decrease while the success rate improves resulting in fewer malpractice suits. For situations where customized device solutions, both internal and external, are applied, the overall recovery time will be reduced, again lowering overall medical costs. When you take this into account along the overall time for preparation actual operation time, the savings can be considerable. As an example, according to a Milliman Research Report (See Appendix H [50]), the average cost of a kidney transplant is currently estimated at ~$334, 000 with well over 50% of that cost related directly to hospital and post-discharge recovery. When combined with an expected increase in demand, by 2030 the estimated cost of the same kidney transplant could be reduced by two-thirds to ~$120,000.

Highlighting another benefit of the technology, 3D printing can be used to establish a cellular based structure for examining drug interaction and cosmetic applications. You would expect that research breakthroughs will come quickly and time to market for revolutionary advancements will further reduce the overall cost of development. In that case the application space is still growing but as a means of studying material interactions, including potential bacterial and viral diseases, the opportunity for inexpensive research is great. Scientists are already using this type of research to study tumor cells in a controlled environment with multiple new drug therapies [51].

A summary of the motivating factors is shown in Figure 10 in a SWOT analysis form.

	Mtls/Mfg	Reg/Ethics	Econ/Cost
Strengths	Single point of development Base technologies and Mtls to build from	Broad application opp. Limit live host for drug testing	Available/supportable market (s) Supplementary Market Significant upside potential Faster recovery times
Weakness	Requires continued advancment Body rejection	Unregulated quality No monitoring Untested impacts Stem cell research	Competition Initial cost and unknown reduction curve
Opportunities	Drug/Mtl interactions Production TPT's Customized Solutions	Super human - equal playing field Patent wars Brings medical to 3rd world	Portable equipment Reduced material cost over time
Threats	Other companies Limited user understanding	After market solutions Oppty's for crime - bio manipulation SkyNet	Other companies Patents

Figure 10. SWOT Analysis

6. Conclusion and Discussion

While we there are four main 3D printing technologies that are applicable to healthcare applications, it was not uncommon to find the 3D printing method combined with other methods [52] to produce a more robust and ideal bioprinted result.

Based upon the research publications in this area, the technology is clearly in relative infancy in the Technology Adoption Life Cycle as shown in Figure 11. Given the wide range of applications in healthcare, cost reduction opportunity and a significant gap between donors and people waiting on organ transplant, there is significant market potential for this technology. The reduced time for drug development will be welcomed both by patients with life-threatening illnesses and pharmaceutical companies who can benefit from the reduced waiting time to take it to market. However, given the sensitivity of healthcare, the pace of growth will be slow given standard healthcare regulatory approvals. The good news is that the FDA is taking a lead as evident by the public workshop and interactive discussion on additive manufacturing of medical devices in October 2014.

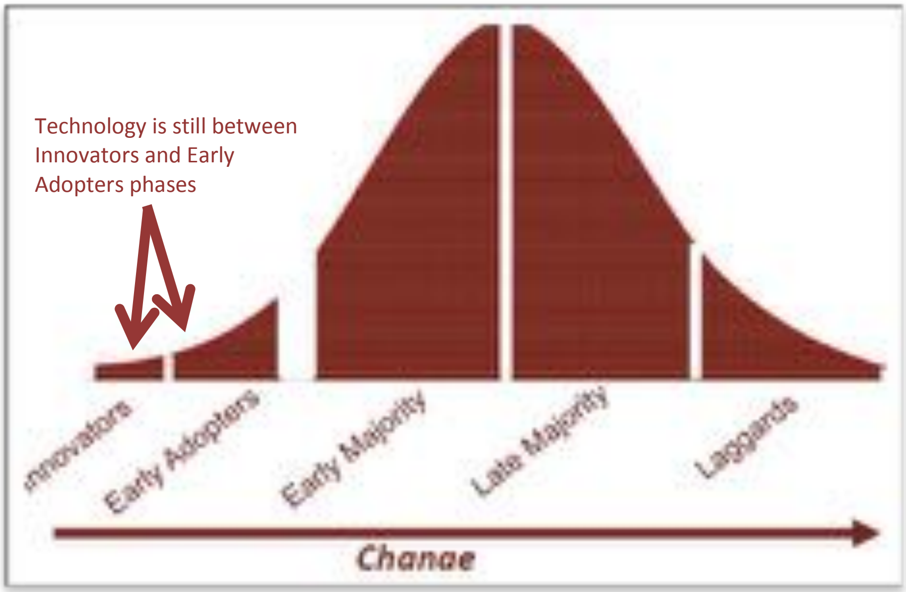


Figure 11. Technology Adoption Life Cycle

Most of the bioprinters today are a product of tight partnership between biological/biomedical and printing technology experts. As examples, the Novogen MMX Bioprinter™ was developed as a partnership between Organovo and Invetech; the OsteoFab® Patient-Specific Facial Device is printed using proprietary materials from Oxford Performance Materials Inc., and their own internal printing division. This highlights that the printing raw materials required for healthcare require highly specialized handling which in turn requires additional customization on the printers. This continued interdependence between raw materials and the printing process expertise could turn into a specialized branch of 3d printing much like computer engineering which focuses on select topics from computer science and electrical engineering branches. This specialization will also result in the creation of new standards that overlaps healthcare and 3d printing technologies.

As bioprinting technology develops, we need make sure Safety and Ethical regulations related to healthcare compliance keep up with managing risks of unregulated manufacturing using 3d bioprinters. If we have a problem with organ trafficking today, will there be a black market for bioprinted organs? If we develop and commercialize an organ bioprinter, will individuals be able to develop organs with no regulations to comply with? We will need physicians or organizations that perform these transplants to influence, be trained on the regulation and compliance requirements.

An immediate beneficiary of the development of 3d printed tissue will be the cosmetic and pharmaceutical industries due to the quicker testing that they can now perform before moving onto any clinical trials.

The majority of publications seem to be related to the materials and manufacturing processes and fewer in the area of regulation and policy. This leads us to the conclusion that we are still trying to identify the right materials and methods for bioprinting organs. This is also supported by the fact that although we have FDA approved 3d printed implants, we didn't find evidence of successful bioprinted organ transplants yet. Once we find the right materials, we are likely to then enter a new phase of this technology in developing the regulations and policies. This will also spur studies into the long-term impacts of bioprinted organs.

7. Future Work

While in this study, we have done a high-level analysis of the types of bioprinting technologies, it would be useful from an engineering and technology management perspective to develop a Hierarchical Decision Model (HDM) in the choosing of the bioprinting technology. This will help researchers and physicians decide which type of bioprinting is ideal to their purpose, whether it be to build tissues, develop organs or supporting implants. The HDM will likely be complex, comprehending materials and manufacturing processes factors discussed in this study.

The technology policy development around bioprinting will also be an exciting and rich area of study for an engineering manager. There are ethical, patient safety and global government regulations. The need for organ transplants are across the world, hence international regulations will add another variation to consider. What are the specific factors that will need to be addressed to prevent the technology from falling down into one of the chasms in the TALC?

The technology forecasting technique applied in this study was perfunctory. An in-depth technology forecast using more rigorous modeling using technology maturity factors will help 3d bioprinter manufacturers develop a better understanding of what areas to focus over the next few years to develop this technology further.

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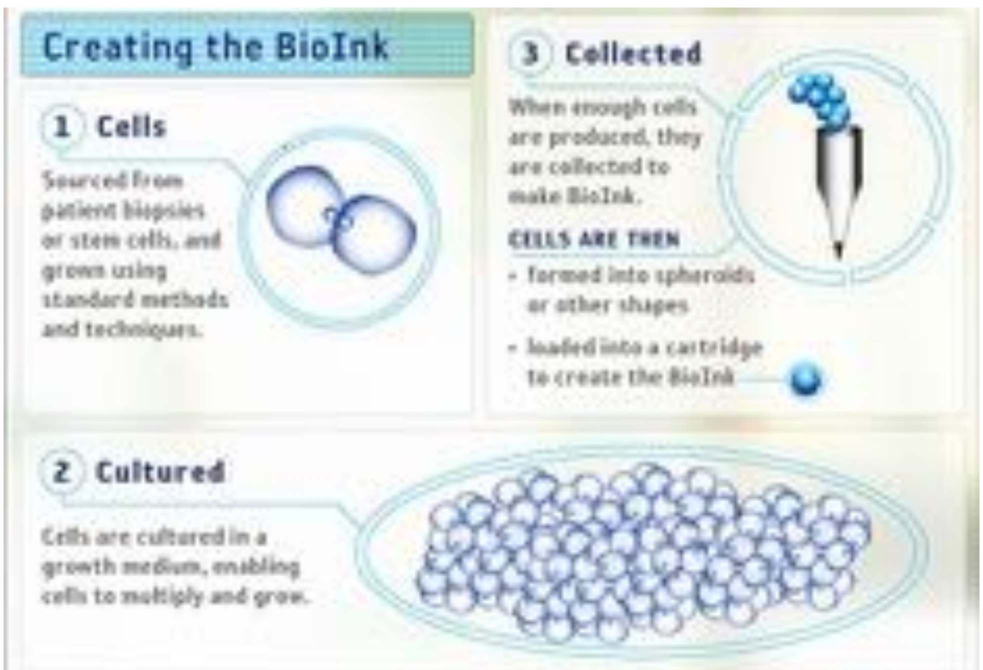
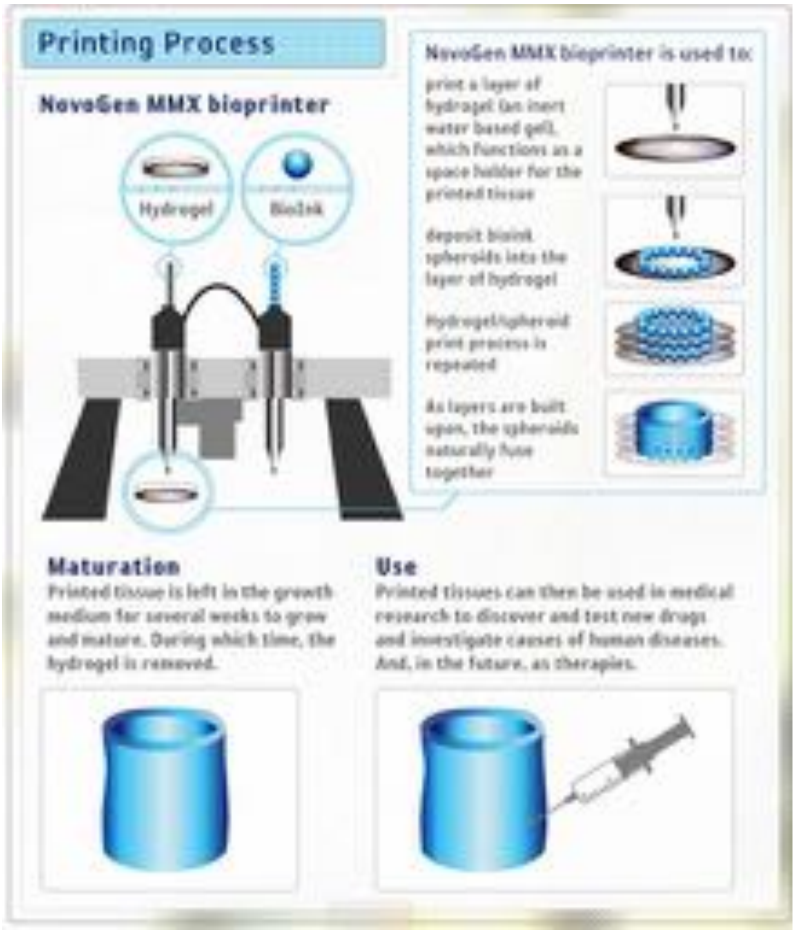
9. Appendix A: Bioprinting Process Overview

A detailed report on the bioprinting process and its application is described by Chuck Tesla using the following illustrations from the online magazine Tumotech.

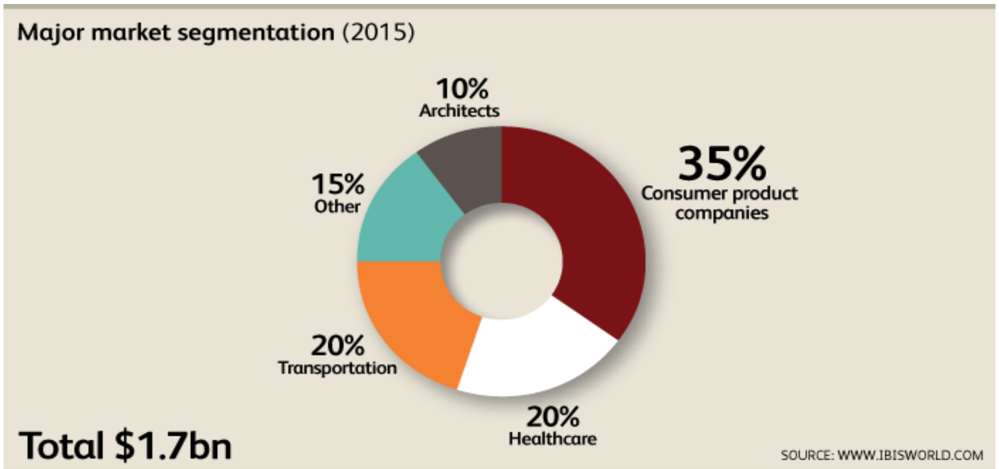




Printing Process
NovoGen MMX bioprinter
Hydrogel
BioInk
NovoGen MMX bioprinter is used to:
print a layer of hydrogel (an inert water based gel), which functions as a space holder for the printed tissue
deposit bioink spheroids into the layer of hydrogel
Hydrogel/spheroid print process is repeated
As layers are built upon, the spheroids naturally fuse together
Maturation
Printed tissue is left in the growth medium for several weeks to grow and mature. During which time, the hydrogel is removed.
Use
Printed tissues can then be used in medical research to discover and test new drugs and investigate causes of human diseases. And, in the future, as therapies.

10. Appendix B: 3D Printer – Industry at a Glance

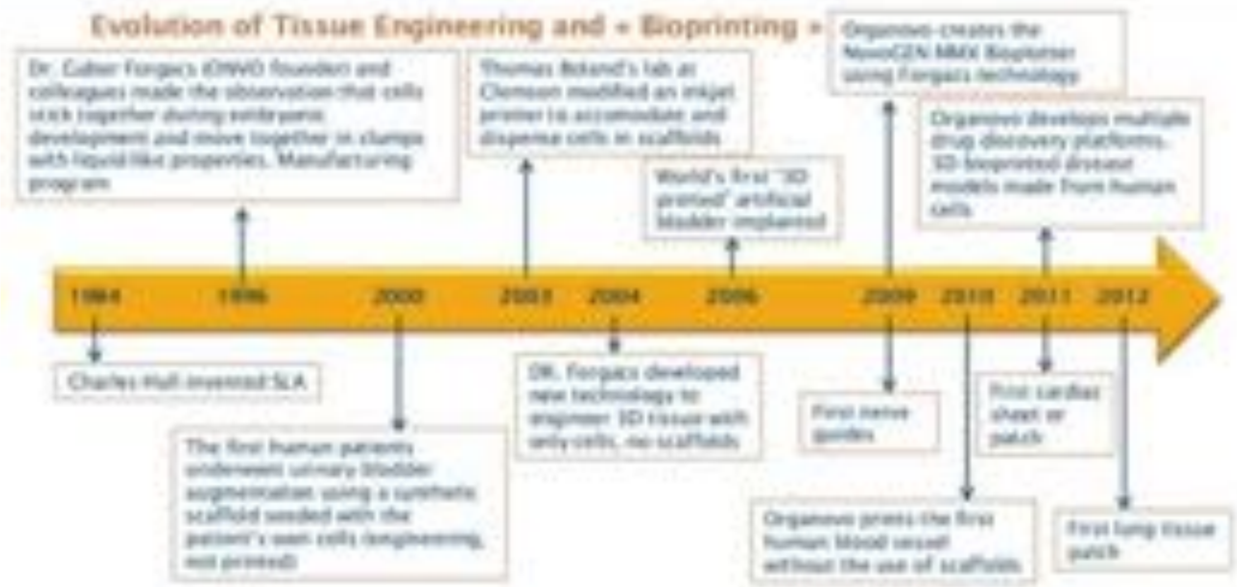
11. Appendix C: Market segmentation of 3D printing for Healthcare



12. Appendix D: Some bioprinting market facts

13. Appendix E: A Case Study – Average Billed Charged per Kidney transplant in 2014

14. Appendix F: Evolution of Tissue Engineering and Bioprinting



15. Appendix G: Organovo Holding stock price - ONVO

RELATED SECURITIES

Symbol	Price		Change	% Change
UTHR	163.84	▲	3.40	2.12%
BA	152.42	▼	-2.33	-1.51%
GE	25.17	▼	-0.47	-1.83%
HON	101.17	▼	-1.97	-1.91%
PFE	33.78	▼	-0.25	-0.73%
ONVO	4.79	▼	-0.56	-10.47%

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16. Appendix H: Transplant Cost Estimates