Title: Forecasting the availability of bioprinted livers for human liver transplant

Course Title: Technology Forecasting
Course Number: ETM 532
Instructor: Dr. Jisun Kim
Term: Fall
Year: 2015
Author(s): Bhaskar Uthanumalliah

ETM OFFICE USE ONLY
Report No.:
Type: Student Project
Note:

Introduction

Problem Statement:

When will 3D bio printed liver be available for a human liver transplant? By surveying experts and analyzing the data using the fuzzy Delphi forecasting method, this work helps to identify the time when it is likely to be possible to use bioprinted livers for human livers transplants.

There are several forces in play that will influence the time when this technology will be commonplace. The main ones are the health care delivery model, advances in research, the health insurance and model, the societal acceptance of stem cell research and the moral, ethical and legal perspectives surrounding organ bioprinting. Predicting the availability of this technology from what is known today is a challenge, and in this work, I am trying to do a forecast using the fuzzy Delphi Forecasting model.

What is Technology Forecasting

Technology forecasting [TF], in general, applies to all purposeful and systematic attempts to anticipate and understand the potential direction, rate, characteristics, and effects of technological change, especially invention, innovation, adoption, and use. One possible analogy for TF is weather forecasting: Though imperfect, TF enables better plans and decisions. A good forecast can help maximize gain and minimize loss from future conditions. Additionally, TF is no more avoidable than is weather forecasting. All people implicitly forecast the weather by their choice of whether to wear a raincoat, carry an umbrella, and so on. Any individual, organization, or nation that can be affected by technological change inevitably engages in forecasting technology with every decision that allocates resources to particular purposes. Formation of research strategies can greatly benefit from TF studies that identify technologies with the greatest potential.

Background:

Organ transplantation is a complex process faced with the low number of suitable donors, problem of organ rejection and requires where complex pre and post-operative care. It is also a very heavy financial, emotional and physical burden for the patients and their families. 10% of the patients die when they are still on the waiting list for organ donors [C.J.E. Watson].

Advances in Medicine [Great Achievements]

The following is the listing of the major achievements in medicine. The list below highlights the rapid expansion of scientific knowledge over the last 100 years. Based on the rate of growth of the medical technologies, it is reasonable to forecast the day when bioprinted organs will be available for human transplants. Given that scientists have already bioprinted the thyroid gland [3DPrint.com], it is reasonable to expect that a more complex gland such as a liver can be bioprinted and used in human liver transplants in the foreseeable future.

1903 First electrocardiograph machine
1927 First modern practical respirator
1930s Artificial pacemaker invented
1933 Kouwenhoven cardiovascular research
1945 First kidney dialysis machine
1948 Plastic contact lens developed
1950s (Late) First artificial hip replacement
1951 Artificial heart valve developed
1952 First successful cardiac pacemaker
1953 First successful open-heart bypass surgery
1954 First human kidney transplant
1950s (Late) First artificial hip replacement procedure
1960 First totally internal pacemaker
1963 Laser treatments to prevent blindness
1970s (Late) Arthroscope introduced
1971 First soft contact lens
1972 CAT or CT scan is introduced
1978 First cochlear implant surgery
1980s Controlled drug delivery technology developed
1981 MRI (magnetic resonance imaging) scanner introduced
1982 First permanent artificial heart implant
1985 Implantable cardioverter defibrillator (ICD) approved
1987 Deep-brain electrical stimulation system
1987 First laser surgery on a human cornea
1990 Human Genome Project

The Promise of 3D bioprinting: [IB Times]

3D bioprinting of human organs will reduce the wait times for patients for organ transplants. The current 3D printing of human organs focusses on the ability to print organs that will help drugs to get to patients by testing out drug toxicity on 3D printed cells faster by reducing the testing time and get liver tissues faster to help people with chronic liver problems.

Over the past year, hospitals around the world have begun talking about their burgeoning use of 3D printing in health care, from 3D printing an entire skull, to rehearsing incredibly complex surgeries and creating implants for reconstructive surgery

"3D printing is revolutionizing every aspect of the medical industry. It saves time, it saves more lives and it improves the efficiency of the surgery as well"- Dr. Muhanad Hatamleh

There are also great hopes for bioprinting, such as 3D printing human cells. The technology is still in its infancy but great strides have been achieved in the past few years. "By replacing all of that with micro tissues, you can then straightaway tune the drugs to humans, and it also allows you to do personalized medicine, because you can use patient-specific cells, and you can work out how a person would respond to a particular medicine and then personalize the medicine for that person". Medical students and doctors are being trained to use 3D printing, especially when it comes to treating major injuries affecting

the head, mouth, jaw, face and neck. Now we are graduating a new generation of doctors who are now totally 100% depending on having 3D medical facilities. Having a 3D facility in any maxillofacial unit is a must. In the past, 3D printing was just an accessory, but now it is a must

Bioprinted organs have the potential to be optimal because they should not induce a toxic or immune response (inflammation), have a low level of transmittable disease risk, have a slow biodegradable scaffold, support normal tissue reconstruction, improve vascularization, and have similar mechanical and physical properties to the natural organ it is replacing (Mironov et al., 2009). If created appropriately, it will be resistant to bacterial colonization and result in normal tissue reconstruction, cellular adhesion, and tissue acceptance. The bioprinted organ will also be able to maintain its structural, mechanical, biological, and metabolic properties similar to that of a normal, healthy organ and sustain the viability of all cells throughout the construct without signs of DNA mutations, cellular apoptosis, cell stress, or degradation. A few advantages for using organ printing include 3-D positioning of multiple cell types, creating tissues with a high level of cell density (leading to accelerated tissue maturation), mass reproduction of engineered tissues, the ability to engineer tissues with densely branched vascular networks, and the ability to include bioactive components in their structure (Mironov et al., 2009). [***Natalie***]

The challenges in human transplant of bioprinted organs

Organ printing is very promising and has the potential to revolutionize medicine. However, it currently still has many limitations. After printing is complete, the constructed tissue's low cell density in comparison to natural tissues is one main drawback (Guillotin & Guillemot, 2011). In order to have a cellular volume fraction and mechanical properties similar to live tissues and organs, accelerated tissue maturation must be developed and perfected. Also, since bioprinting relies on self-assembly for fabrication, the level of guidance during development needs to be determined to create a structure close in architecture to its natural counterpart (Guillotin & Guillemot, 2011). Another challenge is gaining access to a broad spectrum of materials such as progenitor cells, hydrogels, and biomaterials (Graca & Filardo, 2010). The optimal materials will need to be studied for determination, along with creating the resources and funding to perform this research.

Recent advances have enabled 3D printing of biocompatible materials, cells and supporting components into complex 3D functional living tissues. 3D bioprinting is being applied to regenerative medicine to address the need for tissues and organs suitable for transplantation. Compared with non-biological printing, 3D bioprinting involves additional complexities, such as the choice of materials, cell types, growth and differentiation factors, and technical challenges related to the sensitivities of living cells and the construction of tissues. Addressing these complexities requires the integration of technologies from the fields of engineering, biomaterials science, cell biology, physics and medicine. 3D bioprinting has already been used for the generation and transplantation of several tissues, including multilayered skin, bone, vascular grafts, tracheal splints, heart tissue and cartilaginous structures. Other applications include developing high-throughput 3D-bioprinted tissue models for research, drug discovery and toxicology [Nature.com]

The goal of 3D bioprinting of organs: "*Our goal is to engineer organs using a patient's own cells. With this approach, there would be no issues with rejection, and patients wouldn't have to take the powerful anti-rejection drugs that are now required. This is certainly one advantage of customized organs."*

Current industry

[Forbes – No Donor required] 3-D printing has been around in various forms since the 1980s, originally as a means of quickly producing affordable prototypes for the manufacturing industry. Recently, researchers have found some amazing healthcare and biological applications for 3-D printing technology, called bioprinting. As a result, the 3-D printing market for healthcare is predicted to reach roughly 4.04 billion by 2018. From custom prosthetics to living tissue, 3-D printing is a versatile means of providing cost effective and individualized care to patients.

With the advent of 3-D bioprinting, cells can now be dispensed from the printer onto a biologically compatible scaffolding, layer by layer, to create a three dimensional viable tissue. Numerous tissues have been constructed that can be used for a number of clinical applications from transplants to scientific research.

Although 3-D bioprinting is still a relatively new technology, there is notable success within this field with greater implications as the technology develops. We highlight five noteworthy advances in 3-D bioprinting that that could revolutionize the healthcare industry.

Challenges for artificial organs

Blood vessels: One of the primary limitations to building artificial organs for implants has been the lack of vascularization (the ability to transport blood and other materials through blood vessels to individual cells) in order to maintain organ health. However, a Harvard team has developed a method for creating hollow channels that allow blood to flow throughout the organ, essentially functioning as blood vessels. This new development will allow researchers to build thicker, more complex tissues that would otherwise fail.

There are other ethical, moral and religious challenges that need to be addressed as well to make this technology a reality. Use of certain kinds of stem cells, especially embryonic stem cells generates a lot of public attention, sometimes biased based on several factors. Being able to have access to all scientific tools, without overarching legal and moral hurdles will help to accelerate the availability of this technology.

The case against stem cell research [Peter Lachmann)

Stem cell technologies would be very expensive and available only to rich countries and to rich people. Stem cell research would deviate efforts from other health strategies, Interference with the genome involves 'playing God'. Some researchers consider somatic cell nuclear transfer is immoral as it involves creating embryos only to destroy them and that allowing stem cell research is the thin end of a wedge leading to neo-eugenics, 'designer' children, and discrimination against the less-than-perfect. They are afraid that eventually, an 'immortal' population could evolve and that would create its own moral problems.

Case for stem cell research [MayoClinicStaff]

Stem cell research increases our understanding of how diseases occur, generate healthy cells to replace diseased cells (regenerative medicine) and help to test new drugs for safety and effectiveness

Approach of 3D printing of Organs:

Organ printing is defined as "layer-by-layer additive robotic biofabrication of three dimensional functional living macro tissue and organ constructs using tissue spheroids as building blocks" (Mironov

et al., 2009). All variations of bioprinting, synonymous with organ printing, are characterized by 3 main principles. First, bioprinting does not involve the use of solid scaffolds (Graca & Filardo, 2010). Instead, a processable biomimetic hydrogel is used as a suspension to maintain cell placement and aid in tissue fusion and maturation. Secondly, the foundation of bioprinting is based on tissue spheroids and cell aggregates self-assembling into a functional construct (Graca & Filardo, 2010). This fundamental principle is what differentiates bioprinting from other forms of tissue engineering. The third is the basis for processing bioprinted tissues and organs. This involves the simultaneous and continuous dispension of cells and a hydrogel without intermediate steps to form a fully constructed tissue (Graca & Filardo, 2010). With these characteristics, bioprinting stands out as a completely unique type of tissue engineering.

The following are the high level steps involved in organ printing [Atala and Sean V Murphy]

1. A first step in organ engineering – whether it involves 3D printing or other methods – is to get a biopsy of the organ that needs to be replaced.
2. From this biopsy, certain cells with regenerative potential are isolated and multiplied.
3. These cells are then mixed with a liquid material that provides oxygen and other nutrients to keep them alive.
4. This mixture is placed in a printer cartridge.
5. A separate printer cartridge is filled with a biomaterial that will be printed into the organ- or tissue-shaped structure.
6. The structure is designed on a computer using a patient's medical scans.

About the liver: Functions and Diseases

The liver is the largest glandular organ in the body and performs multiple critical functions to keep the body pure of toxins and harmful substances.

An average adult liver weighs about three pounds. Located in the upper-right portion of the abdominal cavity under the diaphragm and to the right of the stomach, the liver consists of four lobes. It receives about 1.5 quarts of blood every minute via the hepatic artery and portal vein.

Functions of the liver:

The liver is considered a gland—an organ that secretes chemicals—because it produces bile, a substance needed to digest fats. Bile's salts break up fat into smaller pieces so it can be absorbed more easily in the small intestine. In addition to producing bile, the liver:

- Detoxifies the blood to rid it of harmful substances such as alcohol and drugs
- Stores some vitamins and iron
- Stores the sugar glucose
- Converts stored sugar to functional sugar when the body's sugar (glucose) levels fall below normal
- Breaks down hemoglobin as well as insulin and other hormones
- Converts ammonia to urea, which is vital in metabolism
- Destroys old red blood cells (called RBC's)

Diseases of the liver:

Common liver diseases include hepatitis infection, fatty liver disease, and cancer, as well as damage from alcohol, the pain reliever acetaminophen, and some cancer drugs.[WebMD - Digestive Disorders Health Center] Liver Enzyme Tests: ALT and AST :ALT and AST are found together in elevated amounts in the blood, liver damage is most likely present [WebMD – Liver Function Tests]

Cirrhosis of the liver occurs when the organ becomes scarred and hardened so that it cannot function properly. This is most often caused by chronic liver disease brought on by long-term alcohol abuse or hepatitis C infection.

Liver dialysis—in which a machine performs the detoxification function of the liver—is still a relatively new treatment, and it cannot support a person longer than a few years. Dialysis is normally used in the time between liver failure and liver transplant surgery.

Liver Function Tests: PT and INR

Besides its functions in metabolism, the liver makes proteins that are essential to normal blood clotting. True liver function tests check the liver's ability to make these proteins. They include:

- Prothrombin time (PT): A test of the time it takes for a blood sample to clot, under specific conditions in a lab; if low levels of clotting factors are present, the prothrombin time is longer.
- International normalized ratio (INR): Not really a test, but a standardized way for all labs to report PT, so their results can be compared accurately with each other.

PT and INR rise in people with severe liver disease because the liver fails to make normal amounts of certain clotting factors. An elevated PT can have many other causes besides liver disease, however. PT is often checked together with PTT (partial thromboplastin time), which is not a liver function test. If PT and/or PTT are elevated, a problem with bleeding or clotting may be present.

Liver Function Tests: Albumin

The liver also makes albumin, an essential protein that circulates in blood. Albumin levels are low in people with severe chronic liver disease, because the liver does not make normal amounts of albumin. However, albumin levels also may fall in a variety of medical conditions. A low albumin level is often temporary, so it is not a reliable way to diagnose liver disease.

Liver Function Tests: Bilirubin

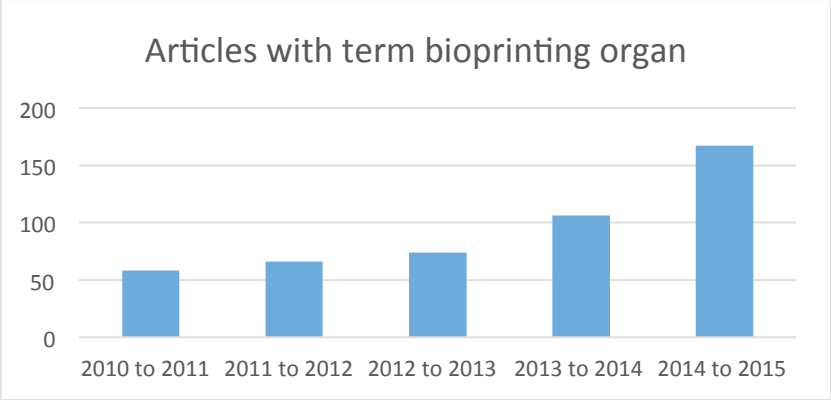
Bilirubin is a waste product from the breakdown of red blood cells. The liver processes bilirubin so it can be excreted in stool. Bilirubin flows through the liver's bile ducts, dissolved in bile. Bilirubin blood levels may be elevated in people with impaired bile flow. This can occur in severe liver disease, gallbladder disease, or other bile system conditions. Very high bilirubin levels cause jaundice, in which the skin and whites of the eyes turn yellow. Bilirubin can be a useful liver function test in people with a known bile flow problem. An elevated bilirubin may also be present in people with a type of anemia, called hemolytic anemia.

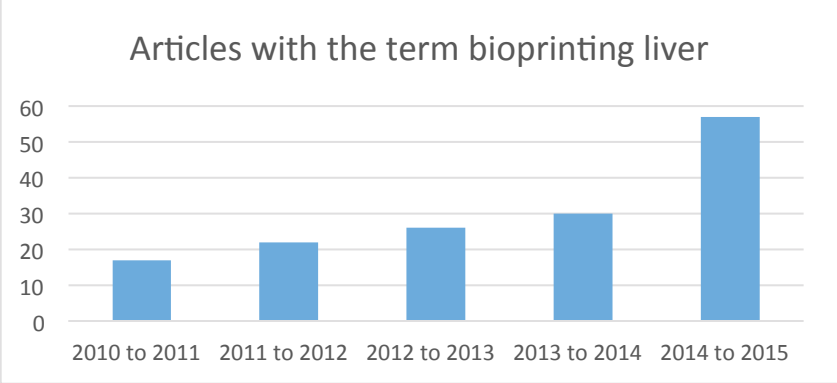
Current Research:

Liver cells: Organovo, the developer of the first 3-D bioprinted liver tissue, has the potential to revolutionize medical research. By making live human liver tissue commercially available, researchers are now able to test the effectiveness and toxicity of medication prior to clinical trials without the possibility of damaging the liver of subjects. Not only does this reduce the time and cost of research, the 3-D tissue also provides vital information to researchers that normal 2-D models would lack. "This gives researchers the kind of tool that they just haven't had in the past. They can't do the kind of experiments on a person that they can do with this tissue in a lab setting." said Michael Renard, executive vice president at Organovo.

Bibliographic Analysis

Based on the data in Appendix B, a graphical representation is shown here. We can see there is a growing interest and momentum in research surround bioprinting organs and bioprinting livers. This is a good indication of the expected growth of technology as there is a high correlation between the number of scientific publications and patents in most of the technologies investigated [Murat Bengisu]





Forecasting Methods

Classification of forecasting methods

One frequently used classification of forecasting methods groups them into four different types:

Extrapolation assumes that the future of a time series is completely captured by the past of that series, which only needs to be extended according to the mathematical law that describes it (trend, cycle, growth curve, and so forth).

Leading indicators assume that the future of one time series is completely captured by the past of another time series, the "leading indicator." A change in the leading indicator will be followed by a corresponding change in the time series to be forecast (changes in the Producer Price Index are a leading indicator for changes in the Consumer Price Index).

Forecasting technology by leading indicators is often refined by observing partial successes or failures, identifying what additional features or developments are required for success, and then undertaking a deliberate search for evidence of achievement of these "missing" elements. That is, the forecaster asks, "If this is a genuine leading indicator, what should be expected next?" The outcome of the search then becomes another leading indicator.

The problem with this forecasting method is that it is inherently qualitative. It cannot provide a quantitative estimate of when a new development will be commercialized or deployed, or what the expected level of performance will be. Despite this shortcoming, however, it is a very powerful method and is used extensively.

Causal models assume that the relevant variables and their linkages are known and can be described in mathematical equations (for example, eclipses of the sun and moon are forecast using causal models). Simultaneous solution of the equations, either in closed form or by computer simulation, then serves to forecast the future values of the variables.

Stochastic methods differ from the others in the nature of the forecast. The other three methods produce a single-point forecast—a single number for the value of the quantity being forecast. By contrast, stochastic forecasts give a range of values for the outcome and the probability distribution over that range (at the racetrack, the bettor is provided with the names of the horses entered in the race, and the odds on each horse, rather than the name of a single predicted winner).

S-Curves [Christensen]

The technology S-curve has become a centerpiece in thinking about technology strategy. It represents an inductively derived theory of the potential for technological improvement, which suggests that the magnitude of improvement in the performance of a product or process occurring in a given period of time or resulting from a given amount of engineering effort differs as technologies become more mature. The theory states that in a technology's early stages, the rate of progress in performance is relatively slow. As the technology becomes better understood, controlled, and diffused, the rate of technological improvement increases. But the theory posits that in its mature stages, the technology will asymptotically approach a natural or physical limit, which requires that ever greater periods of time or inputs of engineering effort be expended to achieve increments of performance improvement.

Usage of growth curves

The assumptions for the usage of the growth curves are that the upper limit to growth is known, the chosen growth curve is the correct one and the historical data yields correct coefficients of the chosen curve.

The Upper limit must be determined from theoretical understanding of physical limitations; if overestimated, curve will rise too slowly and lead to an overly conservative forecast. If underestimated, curve will rise too steeply and one would end up with too optimistic of a forecast. Upper limit set by physics & chemistry of technical approach. Upper limit set by market size (population) or 100%

Growth curves apply to single technical approach and. Growth curves of Market Share can apply to multiple products or technologies

Choice of Growth Curves – Pearl vs Gompertz

Pearl curve is suitable when there is Unexploited potential in early improvement, whereas the Gompertz Curve is suitable when there is no unexploited potential. In the case of the Pearl Curve, Imitation aids adoption, and existing adoption aids further adoption.

'When can we use an S-curve?' In other words, 'When should we address cumulative growth?' S-curves and logistic equations depict natural growth in competition. Although these curves can describe similar behavior in some phases of this development, one of the most important differences is that the Gompertz process is asymmetric, whereas the logistic curve is a symmetric process. Therefore, using an inappropriate growth curve can have a substantial impact on forecasting. The Gompertz curve occurs in situations where there is intense competition between the technologies. [Philip Hans Frances]

Fuzzy Delphi

As one of the long-term forecasting methods, the Delphi method developed by Helmer and his associates has been widely used to date. [Akira] One of the weaknesses of this method is that it requires repetitive surveys of the experts-ordinarily more than twice - to allow the forecast values to converge. The more we repeat surveys, the more costly they become. In addition, the response rate becomes lower, particularly so for a complicated survey. The fuzzy Delphi method eliminates the need for multiple repeated survey of the experts.

Questionnaire

In the new fuzzy Delphi method, the question items that forecast the period of realization consists of:

(1) The period where realization is absolutely impossible, and
(2) The period where realization is certainly possible.
The time between (1) and (2) above is identified as the grey zone where some of the experts believe the technology is possible and some don't. In our daily judgments, we are very often faced with such gray zones and are likely to discard them because of their fuzziness and ambiguity. Considering the semantics of these zones, however, we notice the significance and importance of them in that possibility and impossibility coexist and that the judgment is left to the decision maker as to whether or not a selective judgment is made. Thus, we, now look into such gray zones in more depth.

A portion of the questionnaire is designed to collect the degree of importance, period of realization, and the extent of expertise of the survey participants.

(1) The degree of importance: To be recorded from zero to ten points. From the viewpoint of realization, should the respondent judge that realization is extremely important, then ten points are given? If, on the other hand, realization is not at all important, then zero points are given.

(2) The period of realization: For periods when realization is never possible, "impossible up until 199xx" is recorded, while for periods when realization is absolutely possible, "possible from 19xx".

(3) The extent of expertise: When no expertise exists, zero points are inserted, whereas for extremely high expertise, ten points. Upon summing up the data on the basis of the above taxonomy, in-depth analyses were made.

4.1. Fuzzy Delphi Algorithm via Max-Min normativism in this algorithm, the following steps are included:

Step 1. Construct a table of cumulative frequency distribution, with F~(x): a function that denotes the period of realization with an extremely high degree of possibility, and F2(x): a function that denotes the period of nonrealization with an extremely high degree of possibility. Both Fl(X) and Fz(x) denote cumulative frequency distributions.

Step 2. Both upper and lower quantiles of Fl(x) and F2(x) are obtained as shown at (CI, DO and (C2, D2), respectively. Furthermore, medians corresponding to F~(x) and F2(x) are designated as ml, and m2, respectively. The membership functions denoting 'realizable period' and 'unrealizable period' are Pl(X) that links C1, ml, DD and P2(x) that combines C2, m2, /92, respectively.

In this arrangement, the region where realization is achieved becomes the defined domain [al, bl] of P~(x) and the forecast period for realization X1 (E[a, b]) denotes the period when realization is most possible. In a like manner, the domain of non-realization is defined as [a2, b2] within P2(x) and becomes the forecast period of unrealization. X2 (e[a2, bad denotes the highest membership value out of the non-realization with an extremely high degree.

Step 3. The Max-Min forecast value X* is to be obtained by computing MaxMin(Pl(x), P2(x)). This is the value of the forecast period on the basis of two contrastive periods. The line connecting cl, m, with /92 becomes the membership function which synthesizes both pl(x) and p2(x). We call m a 'cross point', and the defined zone of the membership function a 'gray zone'. Thus, the Max-Min forecast value belongs to the gray zone in which both the 246 A. Ishikawa et al. / The Max-Min Delphi method and fuzzy Delphi method realizable and unrealizable periods show the same value of the membership function. The Max-Min forecast value is obtained by MaxMin(fffx), fz(x)).X*

Fuzzy Delphi will be used: Amongst the different methods discussed here, since the bioprinted liver transplant is a future technology, and there are not known use of bioprinted livers in humans, the use of the Delphi survey method is the appropriate technique.

Questionnaire:

Survey Participants:

Leading experts in the field of transplant were contacted to participate in the survey. They were practicing transplant physicians and surgeons at one of the leading Academic Medical centers in the USA. Their title ranged from Assistant Professor, Associate Professor and Professor. Also a few physicians with over 15 years of service were contacted to respond. A total of 12 responses was collected, amongst 30 survey participants.

About the survey:

A survey was conducted using the SurveyMonkey software. The participants were emailed out the survey and were asked to respond.

Below is the content of the survey questionnaire.

- *About me:* I am currently an employee of OHSU in ITG. I was the data architect for the Transplant System Cognos reporting solution. I am pursing an Engineering and Technology Management graduate level course at PSU. This survey is a part of a project for the course.
- The survey results will be confidential.
- Details about the fuzzy-Delphi method can be found here
- You are required to fill only the following columns, with the green background
    - The period of application, split as 2 columns B-1 and B-2
    - Your comments – Your freeform input on each of these questions is valuable
    - Your Survey comments – Please input your views on the key barriers to be met and thresholds to overcome for bio printed liver transplants to be successful

Survey Questionnaire:

Given the recent advances in 3D bio printing of organs, companies such as Organovo have been making tremendous progress in the bio printing of human organs, including the bioprinted human liver tissues. A thyroid gland has been successfully printed as well.

Based on your vast medical experience, given the landscape of current medical care models, health care delivery institutions, financial payer models, advances in research, collaboration amongst research organizations and industry, legal and ethical frameworks, societal perceptions of stem cell research, what in your opinion, will be

- The year **before** which you think 3D printed livers ***can never be used*** in human liver transplants
    - *Your answer - year =* 20**xx** *in the table below* ***(B-1)***
- The year **after** which 3D printed livers ***will commonly be used*** in human liver transplants.
    - *Your answer - year =* 20**yy** *– in the table below* ***(B-2)***

3D Printed Liver Characteristics	The Extent of Importance 10 = High	The period of application	Your Expertise 10 =	Your comments

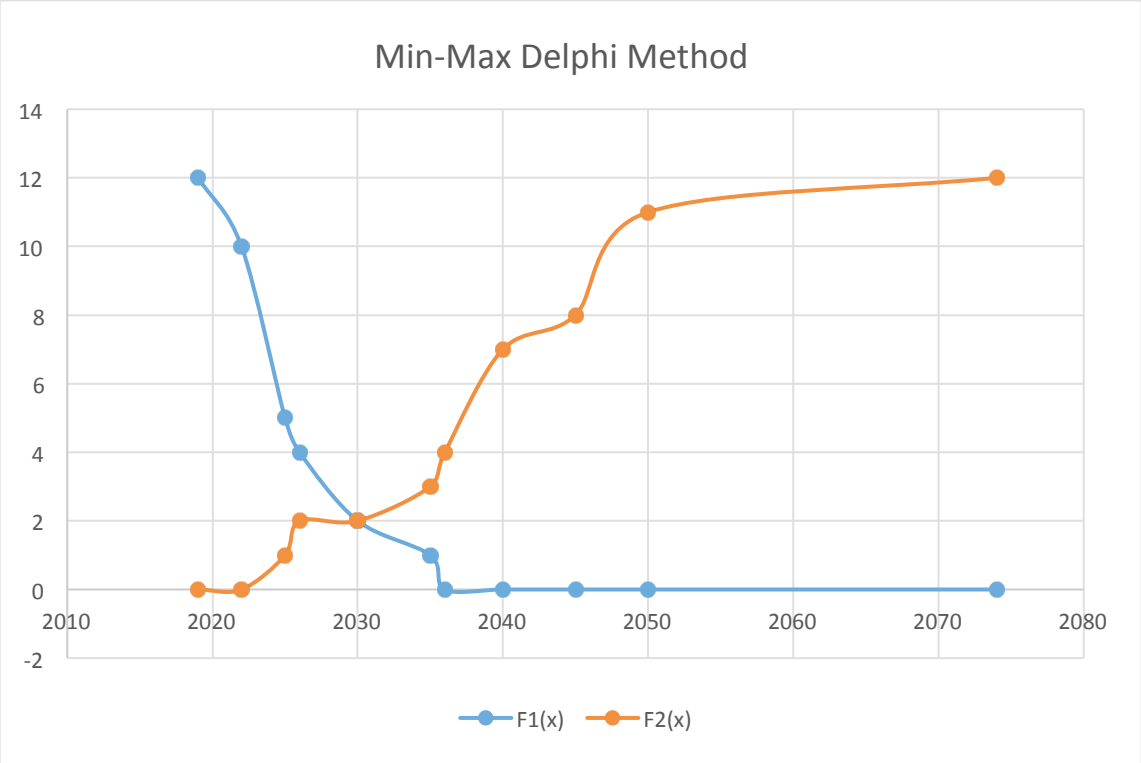
		0 = None			High 0 = None	
			B-1 Definitely Not before Year 20**xx**	**B-2** Definitely after Year 20**yy**		
Product Availability, meeting functional needs	The 3D Printed Liver is commercially available and functions to meet the following needs. • Controls ALT and AST levels • Maintains acceptable levels for Alkaline Phosphatase, 5' Nucleotidase, and GGT enzymes • has acceptable Prothrombin time • makes normal amount of albumin • maintains normal Bilurubin levels		20**xx**	20**yy**		*<Your main concerns>*
Rejection Risk	The 3D Printed Liver Transplant failure rate is less than 25%		20**xx**	20**yy**		
Complication Risk	Risk of other complications with 5 years is less than 25%		20**xx**	20**yy**		
Patient Longevity	After the 3D liver transplant the 75% of patients live for at least 10 years.		20**xx**	20**yy**		

Your Survey comments:

Please feel free to summarize your thoughts on what the key barriers to be met and thresholds to overcome for bio printed liver transplants to be successful

Survey Results - Quantitative

Survey Reponses are shown in Appendix A, along with the cumulative frequency distribution. Using the charting technique discussed in the Max-Min Delphi method of Akira, the following chart was obtained



Based on the above data,

		Median
Not Before 25th percentile	2025	2025.5
Not Before 75th percentile	2030	
Definitely After 25th percentile	2035.75	2038
Definitely After 75th percentile	2050	

Survey Results – Qualitative comments.

The following is the listing of the comments by the survey participants to the question, "*Please summarize your thoughts on what the key barriers to be met and thresholds to overcome for bio printed liver transplants to be successful*". These responses give a qualitative insight to the priority of the different issues facing creating a functional bio printed organ and the transplant to a human body.

- *"Population of printed livers with relevant cell types aggregated in meaningful 3D architecture"*
- *"Based on the current technology, I don't think that a 3D printed liver will ever be suitable for transplantation. In light of this, I cannot quantify the risk of complications, rejections, or longevity. Hope that helps"*
- *"Functionality and cost"*
- *"Vascular and biliary drainage interfaces that allow anastomoses to the recipient's arterial and venous systems and GI tract"*
- *"Actually making a working one"*
- *"Current 10 year survival ~ 55%. Current survivals are going to be your competition to beat."*
- *"safety , fda approval, hla compatibility"*
- *"The risk of complications with current liver transplant is not less than 25% with current practice, there is no reason to believe it would ever be with bioprinted livers"*

Discussion of the Results:

The cross point m occurs between the median of the "Not before data set" = 2025.5 and the median "Definitely after" data set of 2038.As depicted in the diagram, the cross over point is about the year 2030.

So based on the above analysis, we can expect that the use of bioprinted livers for human transplants can be forecasted to occur around 2030.

However, based on the expert's comments, we can clearly see that they are concerned if the 3D bio printed livers will be able to function the same as a natural liver. Once the bioprinted liver meets the acceptable level of functionality, a critical barrier to the use of bioprinted liver in human transplants will be overcome. Then the question of cost and other legal/ethical barriers will only be the barriers to the use of this technology.

Short comings of this Analysis:

Small Data Set: Only 12 results were obtained for this study. Access to the experts in the field of transplant is challenging. There are only a limited number of transplant physicians in the country, mainly in academic medical centers. Getting access to these highly skilled professionals is a challenge.

Extent of Specialization was not a factor: There is another variant of this approach called the FDMFI [Akira Ishikawa] – which involves fuzzy integration using the importance and the extent of specialization of the respondents. It creates membership functions to forecast items and computers the forecast values through fuzzy integration, where the extent of specialization becomes the fuzzy measure. However, given the limited number of responses, and the difficulty in getting access to experts in the field of organ transplants, this method has not been followed.

Appendix A: - Survey Responses

Question: Functional bio-printed Liver Available: The bioprinted liver functions to control ALT and AST levels, albumin and bilirubin levels, maintains acceptable Alkaline Phosphatase, 5' Nucleotidase, and GGT enzyme levels and has acceptable prothrombin time.

Definitely Not Before Year (-B-1 -e.g. 20xx)	Definitely After Year (-B-2e.g. 20yy)
2030	2040
2030	2040
2030	2040
2030	2074
2035	2050
2019	2030
2025	2035
2022	2025
2030	2050
2026	2036
2030	2050
2035	2045

Getting the cumulative frequency distributions for charting

Year	F1(x)	Cum Dist
2019	1	1
2022	1	2
2025	1	3
2026	1	4
2030	6	10
2035	2	12
Year	F2(x)	Cum Dist
2025	1	1
2030	1	2
2035	1	3
2036	1	4
2040	3	7
2045	1	8
2050	3	11
2074	1	12

Appendix B: Bibliographic Analysis

Bibliographic Analysis	
World cat at Portland state university	
bioprinting organ	
2010 to 2011	58
2011 to 2012	66
2012 to 2013	74
2013 to 2014	106
2014 to 2015	167
bioprinting liver	
2010 to 2011	17
2011 to 2012	22
2012 to 2013	26
2013 to 2014	30
2014 to 2015	57

Bibliography

Atala, S. V. (2014). 3D bioprinting of tissues and organs. *Nature Biotechnology*, 773-785. Retrieved from http://www.nature.com/nbt/journal/v32/n8/full/nbt.2958.html

C. J. E. Watson1, *. a. (2012). Organ transplantation: historical perspective and current practice. *British Journal of Anaesthesia*, 29-42. Retrieved from http://bja.oxfordjournals.org/content/108/suppl_1/i29.full.pdf+html

Christensen, C. M. (1992). Exploring the Lmits of Technology S-Curve Part 1. *Production and Operations Management, 1*(4).

Forbes. (n.d.). *Forbes*. Retrieved from http://www.forbes.com/sites/robertszczerba/2015/06/17/no-donor-required-5-body-parts-you-can-make-with-3-d-printers-2/

FRANSES, P. H. (1994). A Method to Select Between Gompertz and Logistic Trend Curves. *TECHNOLOGICAL FORECASTING AND SOCIAL CHANGE*, 45-49.

Graca, B. a. (2010). Vascular bioprinting. *The American Journal of Cardiology, 8*, 141-142.

Great Achievements. (n.d.). Retrieved from http://www.greatachievements.org/?id=3824

Guillotin, B. a. (2011). Cell pattering technologies for organotypic tissue. *Trends in Biotechnology, 29*(4), 183-190.

Ishikawa, A. (1993). The Max-Min Delphi method and fuzzy Delphi method via Fuzzy Integration. *Fuzzy Sets and Systems, 55*, 241-253.

Kerestes, N. M. (2012). *Bioprinting: Is this the Solution to the Organ Transplant Crisis?* University of Toledo. Retrieved from http://utdr.utoledo.edu/cgi/viewcontent.cgi?article=1533&context=graduate-projects

Lachmann, P. (n.d.). Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1083849/

Liver Function Tests. (n.d.). Retrieved from http://www.webmd.com/a-to-z-guides/liver-function-test-lft

Mironov, V. V. (2009). Organ printing: Tissue spheroids as building blocks. *Biomaterials,, 30*, 2164-2174.

Morber, J. (2015, Mar 18). *PBS*. Retrieved from http://www.pbs.org/wgbh/nova/next/body/3d-printed-organs/

Murat Bengisu T, R. N. (2006). Forecasting emerging technologies with the aid of science and. *Technology Forecasting and Social Change*, 835-844.

Nature.com. (n.d.). Retrieved from http://www.nature.com/nbt/journal/v32/n8/full/nbt.2958.html

Russon, M. A. (2015, May 21). Retrieved from International Business Times: http://www.ibtimes.co.uk/3d-printers-are-now-must-hospitals-treating-serious-head-neck-jaw-diseases-1502428

Russon, M. A. (2015, July 3). *International Business Times*. Retrieved from http://www.ibtimes.co.uk/organovo-ceo-3d-bioprinting-organs-will-help-us-get-people-off-transplant-waiting-lists-1509076

Russon, M. A. (2015, 05 25). *International Business Times*. Retrieved from http://www.ibtimes.co.uk/3d-printing-medicine-how-technology-increasingly-being-used-save-lives-1502609

Scott, C. (2015, Nov 4). *3DPrint.com*. Retrieved from http://3dprint.com/103721/3dbioprintingsolutions-thyroid/

Staff, M. C. (n.d.). Retrieved from http://www.mayoclinic.org/tests-procedures/stem-cell-transplant/in-depth/stem-cells/art-20048117

WebMD. (n.d.). *Digestive Disorders Health Center*. Retrieved from http://www.webmd.com/digestive-disorders/picture-of-the-liver

WebMD.com. (n.d.). Retrieved from http://www.webmd.com/digestive-disorders/picture-of-the-liver