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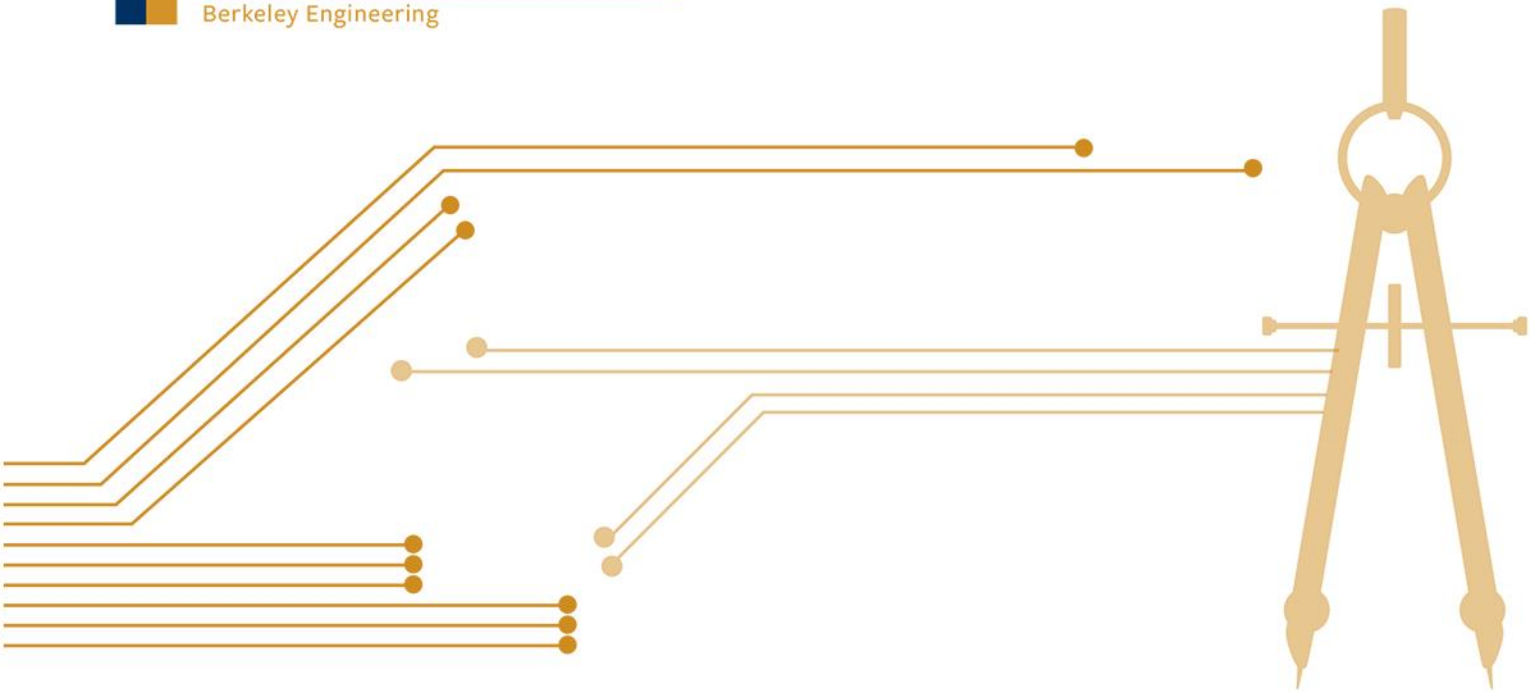

Disruptive Medicine Using 3D Printing

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Date: April 28, 2016

ELPP Project 1

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Introduction

3D printing is a story of hype and disruption in the way objects are traditionally fabricated. Imagine where any three-dimensional object can be automatically fabricated at the click of a button, as we have come to expect from a HP inkjet or laser printer for written media. Due to recent advances in polymerization technologies, reduction of automation (hardware/software) costs, three-dimensional printing of plastics, metals and even bio-materials 3D printing is becoming a practical, commercializable reality. This new capability has disrupted the traditional thought process on how an object is conceptualized, designed, and fabricated. The 3D printing hype has been easily perpetuated as an obvious extension of 3D CAD, and the easily grasped concept of printing 3D CAD objects.

However, the hype has been moderated (at least with respect to market capital valuation of 3D printer equipment companies) as the viability of 3D printing has gained traction in niche areas, and it no longer appears that additive manufacturing easily disrupt many traditional manufacturing methods.

One area where 3D printing makes perfectly good sense is for medical applications. 3D printing excels for applications that require highly customized parts produced in low volume (See Figure 1).. (Conventional manufacturing has a natural advantage of scale due to amortization of upfront cost over mass produced items.) Because humans are physiologically and biologically unique, there is natural synergy for 3D printed production of parts that is personalized to each individual in medical applications.

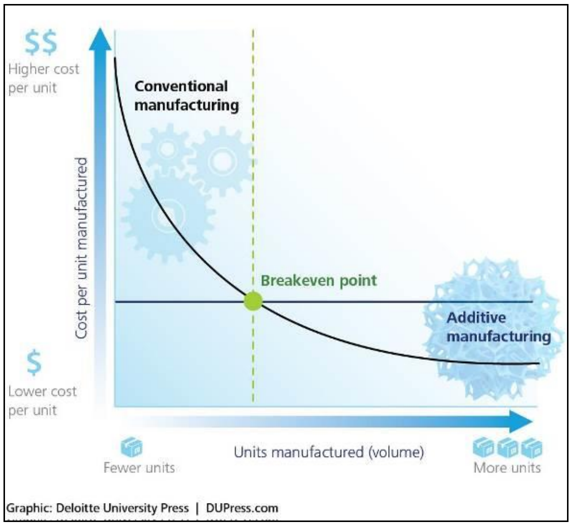


Figure 1. Comparison of fabrication cost per unit as function of units manufactured between conventional manufacturing versus additive manufacturing. While conventional manufacturing relies on scale to reduce manufacturing cost, additive manufacturing does not have the overhead depreciation required whether one unit is fabricated or hundreds of thousands of units. (credit: http://dupress.com/articles/dr14-3d-opportunity/)

Because 3D printing for medical applications is a story about innovation and disruption, we will be using an adaption of the "Three Horizons of Innovation" model by Baghai, Coley and White (See Figure 2). The model suggests companies can be deploying different types of innovation, driven by their maturity of business, where:

- Horizon 1 describes businesses that are focused on execution around a well-defined business plan. The market is perfectly understood and its products are well defined.
- Horizon 2 describes businesses that is in pursuit of probability, where opportunities are typically in new channels that leverage existing technologies or existing channels with new technologies.
- Horizon 3 describes businesses that is in pursuit of possibility. There is no clear business model nor is there clarity on the market. The risks are huge, but herein lies possibility of equally huge rewards.

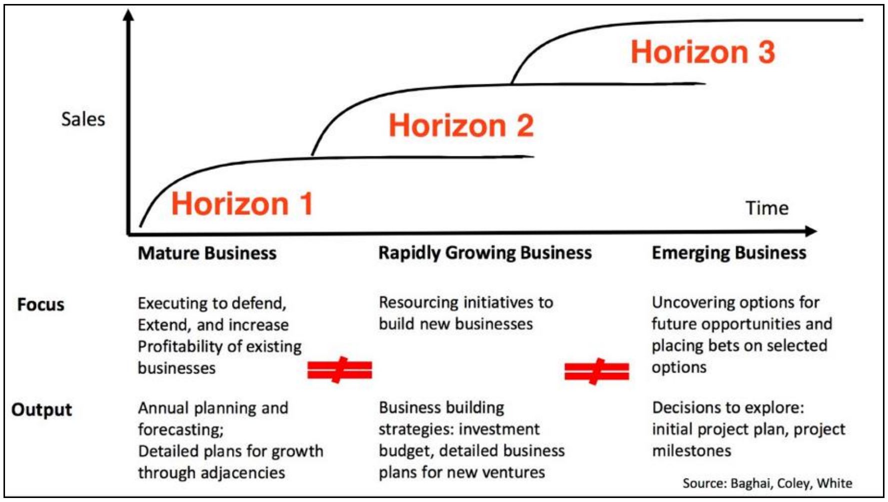


Figure 2. Three horizons of innovation as a function of business maturity. (Credit: https://steveblank.files.wordpress.com/2015/06/three-horizons.jpg)

The three horizons model is typically used to describe businesses within a single company. In this report, we will adapt this model to describe, not a single company's endeavors, but to advocate the levels of innovation maturity of businesses across the spectrum of companies in the area of 3D printing for medical applications. This report summarizes research into three different companies, each as an example of each innovation horizon. We will present how each one plans to use 3D printing to create new opportunities, while disrupting the conventional products/processes.

Horizon 1: Invisalign "The Pursuit of Certainty"

In Horizon 1, the Company has a known business model, with established customers which the Company understands fully. At this point, the Company is focused on process innovation seeking improvements in yield, throughput and cost of ownership. As a company that has found disruption in displacing conventional wire-and-bracket product for malocclusion, Invisalign has demonstrated a solid business model. They had a stock value of 16.88 in Jan 30, 2001, and generally increasing stock price to a 68.90 on march 18, 2016. Gross income has steadily risen from 359Million FY2011 to 646Million in FY2015. Gross margins are held steady at 75% over this time frame as well.

A Short History of Modern Braces

The modern method of attaching brackets to each tooth for adjustments in orthodontics surfaced during the 1970s when formulations of adhesives were made commercially reliable for this application. Arch wire is run through each of the brackets to be tensioned, which applies pressure to each bracket (and tooth) that adjusts the position of each tooth over time (See Figure 3).

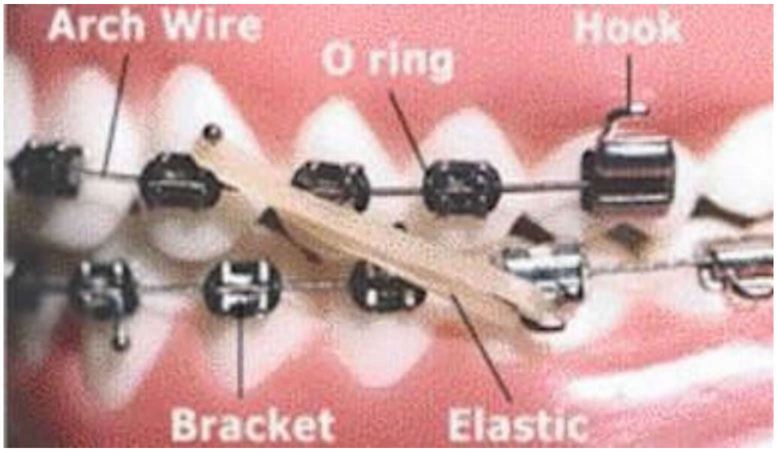


Figure 3. Components that make up bracket-and-wire braces. Credit: http://cognataorthodontics.com/about_braces.html

Other minor advances were made to enhance comfort and aesthetics with next generation brackets for one who wears the braces, such as self-ligating brackets or changes in bracket material from metal to ceramic. Clients were left wanting, since these advances in teeth alignment technology still left their mouths full of visible metal wires.

By mid-1970s, Dr. Kurz of Beverley Hills, California and Professor Kinya Fujita independently developed a novel method called the lingual method which moves brackets from the visible face of the tooth to the interior face of the tooth that allows the client to hide the orthodontics (See Figure 4). This “invisible” braces had varying levels of success from country to country, as it took specialized training in order to treat patients in such a way.

Figure 4. The lingual method moves the brackets and wires to the inside face of the teeth to enhance aesthetics from the front side. (Credit: http://www.archwired.com/HistoryofOrtho.htm)

Story of Disruption

Just like how commercialization of high performance adhesives paved way for mounting of brackets used in braces, advances in 3D printing enabled the next generation of orthodontics. In late 1990s, Zia Chishti and Kelsey Wirth (graduate students from Stanford's MBA program) realized that plastic retainers can make minor adjustments to teeth alignment. They created Align Technologies that took this insight into a product predicated on making minor teeth alignment using a series of clear plastic retainers (or trays) which is customized to the clients' teeth and his stage of adjustment using digitized three-dimensional representation of his teeth. Instead of making a custom mold to generate each retainer—a viable, but more expensive method, each mold were directly fabricated from the digitized model of the clients teeth by additive manufacturing, or more commonly known as 3D printing. The fabrication of the aligners were then thermoformed from the 3D printed mold. See Figure 5.

This is a story of disruption (See Figure 6 for comparison between traditional braces and Invisalign aligners) as the synergy of technologies, in this case modern CAD and additive manufacturing, changed completely how patients suffering from malocclusion can bravely smile while undergoing treatment for teeth alignment.

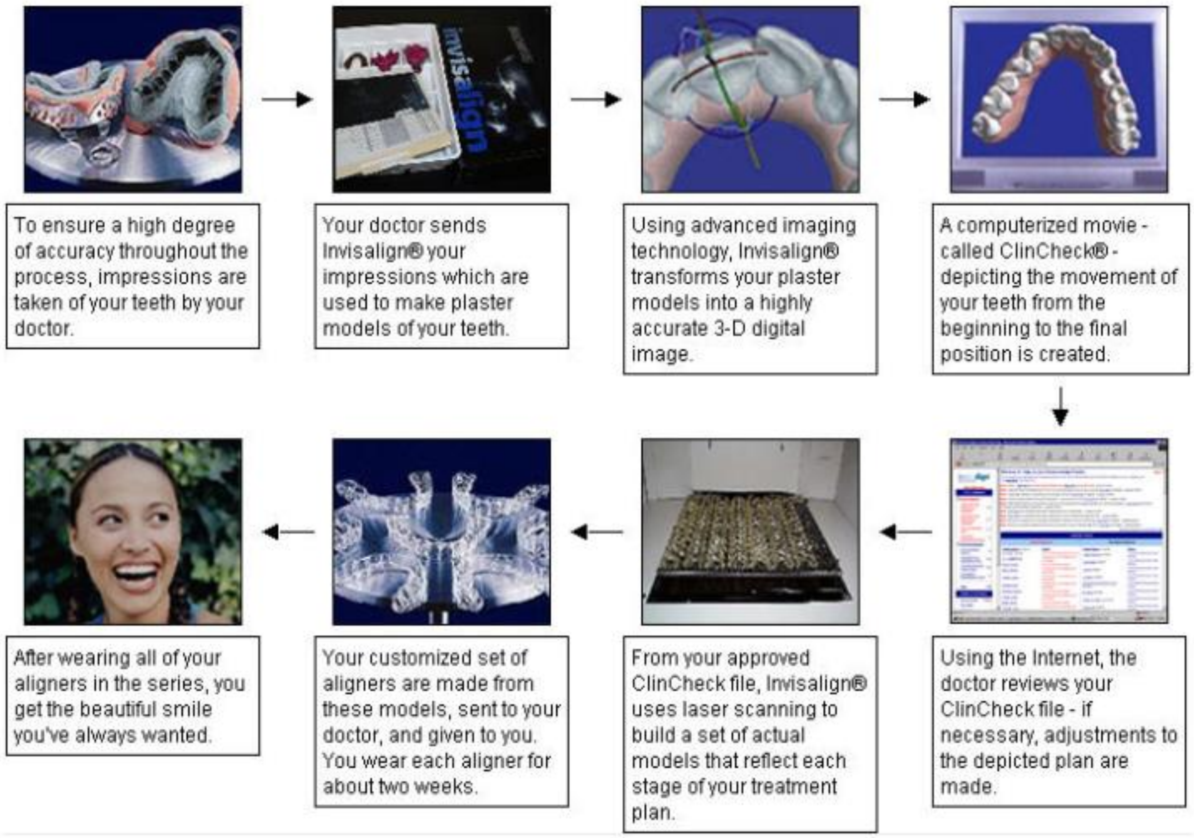


Figure 5. The high level process flow to generate Invisalign aligners for the patient.

Figure 6. Comparison between traditional braces and Invisalign aligners. Credit: Align Technologies

Plastics Printing and Scanning

Technologies used in production of the clear aligners include the 3D printer and the scanner that converts physical teeth representation into a digitized model. In the case of the aligners from Align Technology, they are fabricated in a process called stereolithography—a subcategory of 3D printing of plastics. Stereolithography is done by the following process:

The digitized model of the object to be printed, in most cases an STL file, is loaded into the SLA printer. The printer preprocesses the STL file by "slicing" the three-dimensional model into two-dimensional layers of a finite thickness. Using these datasets for each layer, the printer solidifies material one layer at a time to each other—not much different than stacking layers of cake into a final masterpiece. The printer mechanical architecture includes the following components (See Figure 7):

1) The UV laser and its optical elements,
2) The platform elevator,
3) Liquid level detection module,
4) And the sweep arm

The platform starts by moving into position, such that a precise layer of photocurable resin is presented directly above the platform. The sweep arm traverses across the surface of the resin to planarize the surface. UV laser is then directed to sweep across the two-dimensional representation of the part that make up that layer of the object. UV cures only the irradiated portion of the resin, solidifying the resin to the platform. This process is repeated for each layer, as the new layer is solidified to the layer before it, until the complete object is printed.

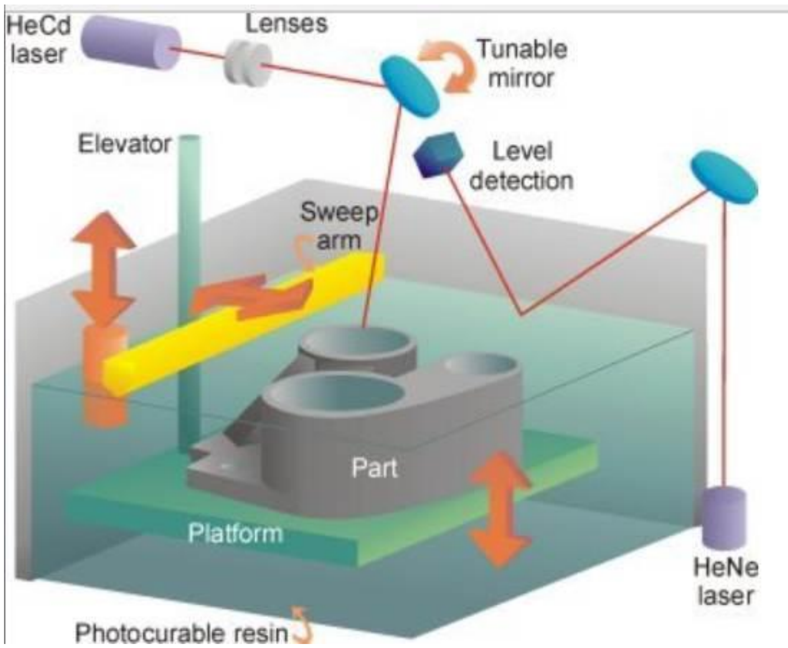


Figure 7. Stereolithography 3D plastics printer decomposed into its major architectural elements.
(Credit: http://www.princeton.edu/~cml/assets/images/mems02.jpg)

The Business Case

Align Technology's primary business is in products and services for their Clear Aligner, Invisalign System. This segment produces 95% of total revenue for the company. Their gross margins for this segment is very healthy at ~75%, proven to be sustainable over the past five years. The existing business model is well established and works. Innovations for this segment will be around innovations in processes that optimizes for operation parameters such as yield, throughput and cost of ownership. In this section, we look at six elements that explains why the Invisalign System is a successful business segment for the company.

a. **Is there an unmet meed?** Invisible braces provide those who suffer from malocclusion a solution which minimizes the impact of aesthetics, typical of conventional methods, such as wire-based braces. Alternatives include lingual method, also by the wire-based braces, mounted on the inside face of the teeth.

b. **Is there a big enough market?** Because the manufacturing cost of each personalized aligner does not scale with quantity, patient costs will remain somewhat high and out of reach for persons of modest means. Aggregating total population of the top 20 countries by GDP, there are approximately 4.4 billion people in 2015. At a cost of $10k per person, one can estimate the total available market is $44 billion. This is a terrific market size.

c. **Does this product have differentiated positioning?** While conventional braces exist, and have done a perfectly fine job of teeth alignment for malocclusion patients, it is not a solution for everyone, as there are patients who desire an option which minimizes the impact of aesthetics while going through treatment. This positions the Invisalign product to be superior to alternatives (See Figure 8). In addition, the Invisalign product is also very easy to use and to maintain during the treatment process. The aligner is worn 20 hrs a day, and does not require a professional to remove. Also, day-to-day maintenance and cleaning is far superior with the Invisalign product, as there are not wires or small crevices to keep clean.

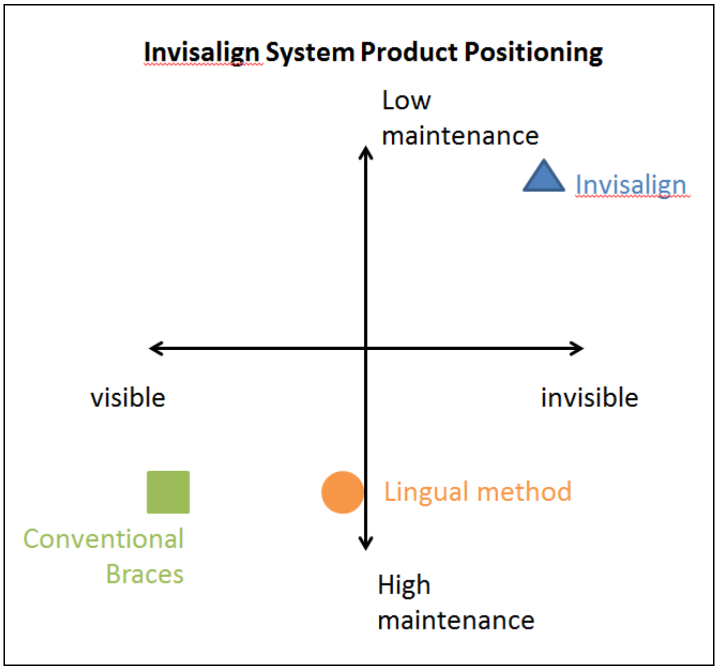


Figure 8. How is Align Technologies positioning their Invisalign aligner product against alternatives?

d. **Is there a scalable business model?** Align Technology has a business strategy of growing both geographically, as well as with their market segment. Their international business is growing well, with focus in Europe and Asia. They plan on expanding their market segment of adults and teens by innovating solutions that enable Invisalign treatment to more challenging cases, which were limited to wire-and-brackets.

e. **Why Align Technology**? Align Technology has secured a strong brand recognition that strengthened adoption rates with dental professionals over time. They have a strong portfolio of products that self-perpetuate their Invisalign product (such as their scanning and CAD integrated software), innovation (releasing multiple generations of Invisalign products—most recently tooth colored buttons that enhance biomechanical advantage in teeth adjustment, and a strong IP portfolio including 384 US patents, 276 international patents and 236 pending applications.

f. **Why now**? Custom invisible braces is truly a unique product. No manufactured aligner is the same as the next one. Convergence of 3D printing technologies, materials compatibility, powerful software solutions in CAD/CAM, really enables the customization-to-cost ratio, giving this product a practical value which may not have been possible at an earlier point in time.

Horizon 2: ConforMIS for Knee replacement industry "The Pursuit of Probability"

Knee replacement industry landscape

When a patient cannot conduct the normal activities such as sitting, lying, walking, climbing stairs due to the damage on the patient's knee by diseases, injuries, or overuse, surgeons first consider non-surgical treatments like medication and usage of supports to walk. However, if such treatments are no longer useful to the patient, total knee replacement surgery is considered as an option. It is a safe procedure to relieve pain, correct leg deformity, and help the patient resume normal activities. The knee replacement industry has been dominated by commodity products for mass production. With advances of technology, however, custom products for personalization are getting economical and more attractions.

Causes of Knee Pain

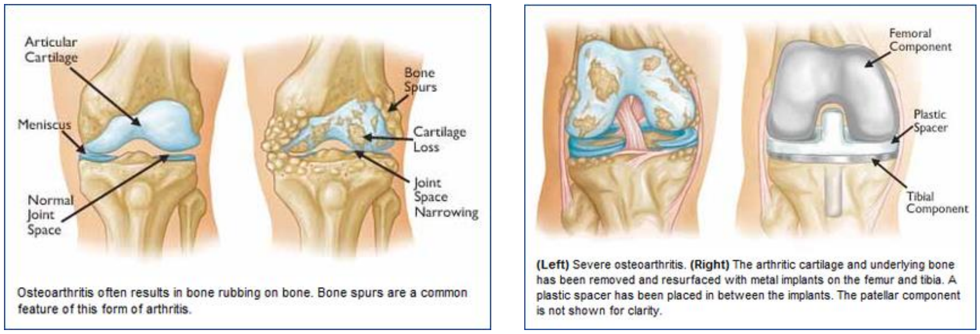
The most common cause of chronic knee pain and disability is arthritis. Wearing is common in the old generation while injury and infection can cause this symptom in the young generation as well. Moreover, severe sport activities and obese due to excessive nutrition accelerate the symptom.

Figure 9. Causes of knee replacement surgery

Although there are many types of arthritis, most knee pain is caused by just three types: osteoarthritis, rheumatoid arthritis, and post-traumatic arthritis[1].

- **Osteoarthritis** - This is an age-related "wear and tear" type of arthritis. It usually occurs in people 50 years of age and older, but may occur in younger people, too. The cartilage that cushions the bones of the knee softens and wears away. The bones then rub against one another, causing knee pain and stiffness.
- **Rheumatoid arthritis** - This is a disease in which the synovial membrane that surrounds the joint becomes inflamed and thickened. This chronic inflammation can damage the cartilage and eventually cause cartilage loss, pain, and stiffness. Rheumatoid arthritis is the most common form of a group of disorders termed "inflammatory arthritis".
- **Post-traumatic arthritis** - This can follow a serious knee injury. Fractures of the bones surrounding the knee or tears of the knee ligaments may damage the articular cartilage over time, causing knee pain and limiting knee function.

[1] http://midamericaortho.com/knee-replacement



Osteoarthritis often results in bone rubbing on bone. Bone spurs are a common feature of this form of arthritis.

(Left) Severe osteoarthritis. **(Right)** The arthritic cartilage and underlying bone has been removed and resurfaced with metal implants on the femur and tibia. A plastic spacer has been placed in between the implants. The patellar component is not shown for clarity.

Figure 10. Types of arthritis[2]

Total Knee Replacement Technologies

In United States, there are over 700,000 knee replacement surgery performed every year[3]. Knee replacement industry has grown by 8.64% CAGR and the global market size is expected to reach $15B/year by 2018[4]. As the average life expectancy is extended, aging related knee preplacement will be more demanding.

[2] http://orthoinfo.aaos.org/topic.cfm?topic=A00389

[3] http://premierortho.com/blog/partial-knee-replacement-vs-total-knee-replacement/

[4] https://www.linkedin.com/company/articulate-labs

Figure 11. Market size of knee replacement for obese[5] (dailymail.com by Matt chorley at July 2014)

Total or Partial Knee Replacement

The knee replacement can be done totally or partially depending on the patients' condition. A partial knee replacement is less invasive surgery which nearly always results in decreased blood loss, less pain, and quicker recovery. Unfortunately, partial knee replacements are only recommended in a limited number of cases. When there is a possibility that a patient's knee problems will get worse over time, which is usually the case, a partial knee replacement patient may eventually need a total knee replacement. In contrast, total knee replacement patients will almost certainly gain significantly more flexibility than they had before surgery, and their knee pain will be dramatically reduced or even eliminated[6]. For this reason, our focus in this report is on the full replacement technology.

Traditional Total Knee Replacement Surgery

The accuracy of alignment in conventional TKA (Total Knee Arthroplasty) depends on the skill of the surgeon and the anatomy of the femur and tibia. Correct location of crucial alignment

5

6 http://premierortho.com/blog/partial-knee-replacement-vs-total-knee-replacement/

landmarks (centers of the femoral head and ankle joint) for determination of the mechanical axis can be difficult to achieve[7].

Computer Assisted Navigation Surgery

Computer-assisted TKA has been developed to improve alignment and implant positioning, to increase accuracy and reproducibility of the operative technique, to enable real-time kinematic analysis and soft-tissue balancing, and to reduce the risk of fat embolism and blood loss by not entering the intramedullary space. It is especially advantageous in obese patients or those with severe preoperative mal-alignment, in whom identification of anatomic landmarks and soft-tissue balancing can be particularly difficult[8].

Custom Knee Replacement Surgery

Custom Fit Total Knee Replacement Surgery is the newest technology in total knee replacement. The process starts several weeks before the surgery with an MRI/CT scan. The MRI makes precise measurements of the knee. Computer software transforms that MRI image into a 3-D model of the arthritic knee and then virtually corrects any deformity to return the knee to its pre-arthritic state. A computerized 3-D image of the implant to be used at the time of surgery is then matched to the anatomically correct knee model. This helps determine the correct implant size and placement based on that patient's normal knee alignment. Using all this information, a set of custom cutting guides is then created for use during the individual surgery. Each knee is unique and each set of MRI computer matched custom surgical guides is one of a kind[9].

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[7] ETH Ek, MM Dowsey, LF Tse, A Riazi, BR Love, JD Stoney, PFM Choong, Comparison of functional and radiological outcomes after computer-assisted versus conventional total knee arthroplasty: a matched-control retrospective study, Journal of Orthopaedic Surgery 2008;16(2):192-6

[8] Same as 7

[9] Same as 7

Emerging 3D Knee Technology

Market Needs[10]

$3.5K – $4K	**Price***	$6K
12-15 years	**Endurance***	20-25 years
2% serious, 20% unsatisfied	**Patient Satisfaction****	
Limited size and quantity	**Inventory**	On-demand

Table 1. comparison between conventional knee replacement and 3-D printing[11][12]

In traditional knee replacement surgery, the surgeon selects an "off-the-shelf" implant from a range of standard fixed sizes, and then has to make the necessary adjustments to fit the implant to the patient during the procedure. Because off-the-shelf knee replacements aren't designed to your specific anatomy, surgeons have to compromise on implant fit.

This compromise may result in having implant overhang (implant hangs over the bone) or underhang (the implant is too small, leaving the bone exposed and uncovered). It could also result in an implant that isn't aligned properly. Clinical studies have demonstrated that these compromises on fit can cause residual pain after surgery. As a result, about 20 percentage of knee replacement patients are not satisfied with the implants and around 2 percentage of patients had serious symptoms like blood clog after surgery.

In addition, such misalignment accelerates the wearing and shortens the lifespan of implants. Traditional implants are expected to use for 12-15 years even though many cases are reported

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[10] http://www.conforMIS.com/customized-knee-implants/

[11] http://www.star-telegram.com/news/local/community/arlington/article3851110.html

[12] http://www.healthline.com/health/total-knee-replacement-surgery/outcomes-statistics-success-rate#1

that the implants last more than 20 years. The old patients implant the first knees around their 60-70's and they highly likely undergo another surgery during their life time.

For example, Zimmer, a leading knee implant supplier, had several recalls and law suits recently. Duron Cup Hip in 2008, 70K MIS tribal devices in 2010, 40K NexGen Knee devices in 2014, and 11658 Persona knee devices in 2015 were recalled.

ConforMIS Technology[13]

ConforMIS does something that believes no other knee implant manufacturer has done. They put the patient at the center of implant design. By combining advanced 3D imaging technology with the latest manufacturing capabilities, they customize each and every implant to the patient's unique size and shape.

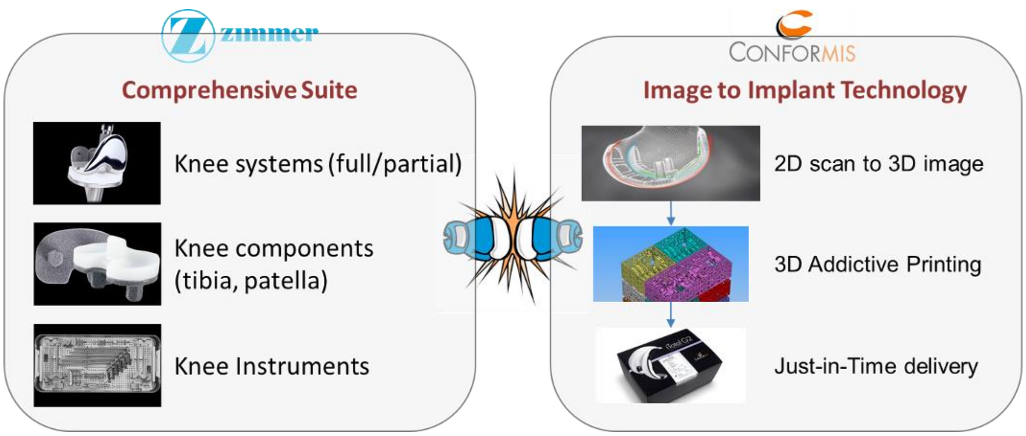


Figure 12. Technology comparison between Zimmer and ConforMIS

ConforMIS introduced a new technology called "image to implant technology" based on 3D printing technology. As shown in Figure 4, the technology consists of 3 main phases: 1) 3D image

[13] Same as 10

construction from 2D CT scan, 2) 3D additive printing for implants and tools, and 3) just-in-time manufacturing and delivery. 20% less bone removal: during the procedure must remove enough bone and tissue to achieve the best fit possible.

iFit® Design

ConforMIS implants and instruments are designed based on the patient's CT scan. An automated design process uses proprietary algorithms to map the articular surface of the joint in three dimensions. The software uses that information to design the implants and instrumentation that will match precisely to the 3D model of the knee, correcting the data for any underlying arthritic deformity such as bone spurs, cysts or flattening of the joint.

iFit® 3D Additive Printing

Disposable, patient-specific iJig® instrumentation is manufactured using the latest in 3D printing technology. Patient-specific instruments for every step of the procedure is developed on demand basis. In addition, the mold for implants is also built using the 3D printing technology.

iFit® Just-in-Time Delivery

Just-in-time manufacturing and delivery capabilities is one of the unique capability of ConforMIS. A single-use kit is delivered a few days before surgery, removing the inventory from hospital shelves. This also allows for rapid design improvements that can be implemented immediately. In addition, iJig instruments are shipped with the ConforMIS knee and arrive fully sterilized. So, the instruments are disposable and hospitals can reduce the risk of infection due to repeated sterilization. Finally, an operation room only one tray of ConforMIS package instead of 9 different trays of instruments for each implant surgery.

Technology Competitiveness

Company	Zimmer	ConforMIS
Mkt CAP	20.78B	383M
Product	Joint (Knee, Hip, etc) replacement	Knee replacement
Knee replacement solution	Persona Knee	iFit Total Kits
Technology	Analytics morphologic knee implant	CT scan to 3D Printer
Materials	Trabecular Metal Tibia – Bone like stable fixation with modular components	• cobalt chromium molybdenum • Ultra high molecular weight polyethylene (UHMWPE) or highly crosslinked vitamin-e infused UHMWPE (iTotal only).

Table 2. Technology comparison

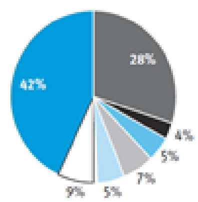
Disconnection of Market Growth

Even though ConforMIS technology has strong momentum and benefit to patient, its growth limited over the years. From SEC financial report, ConforMIS total revenue increased from 34M to 44M in 2015, However, market revenue percentage was quite less than 2.2% compared to Zimmer while Zimmer's total knee revenue was 1,966M in 2014. Noticeably, ConforMIS operation spending have been increased which led net loss over the years and reached to 41M net loss in 2014.

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2015	2014	2015	2014
Revenue				
Product	$ 13,490	$ 12,002	$ 43,953	$ 33,975
Royalty	404	—	3,863	—
Total revenue	13,894	12,002	47,816	33,975
Cost of revenue	10,340	7,351	30,392	21,961
Gross profit	3,554	4,651	17,424	12,014
Operating expenses				
Sales and marketing	10,225	7,083	29,563	22,541
Research and development	3,885	3,969	12,218	11,163
General and administrative	5,656	3,927	16,790	11,775
Total operating expenses	19,766	14,979	58,571	45,479
Loss from operations	(16,212	(10,328	(41,147)	(33,465

Table 3. ConforMIS financial summary

Sales by Product Category



	2010	2011	2012	2013	2014	Reported	Constant Currency(1)
Reconstructive	$3,210	$3,355	$3,350	$3,434	$3,496	2%	3%
Knees	1,798	1,836	1,834	1,910	1,966	3%	4%
Hips	1,262	1,356	1,342	1,330	1,326	0%	1%
Extremities	150	163	174	194	204	5%	6%
Dental	219	248	238	239	243	1%	2%
Trauma	246	286	308	316	317	0%	2%
Spine	234	225	209	202	207	2%	3%
Surgical & Other	311	338	367	432	410	-5%	-3%
Consolidated	$4,220	$4,452	$4,472	$4,623	$4,673	1%	2%

Table 4. Zimmer financial summary

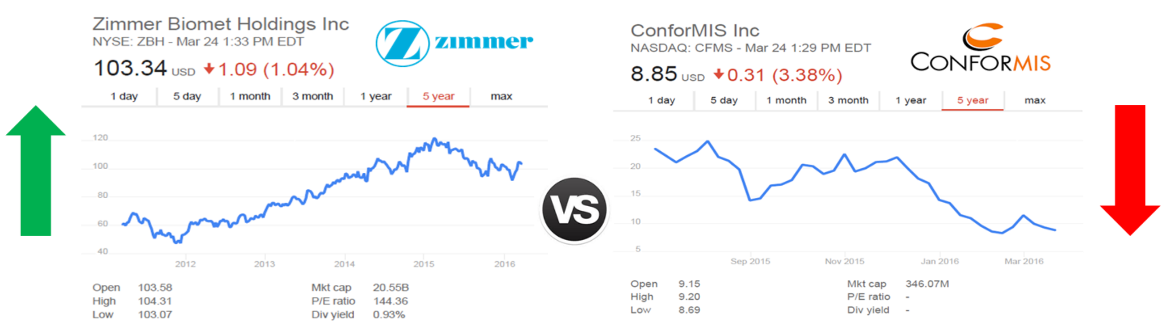


Figure13. stock market trend for Zimmer and ConforMIS

Business Suggestion

Knee Replacement Eco-system & Subsidy Strategy.

Figure 14. Healthcare ecosystem[14]

The healthcare "system" is now better understood as an ecosystem of interconnected stakeholders, each one charged with a mission to improve the quality of care while lowering its cost. To ensure patient safety and quality care while realizing savings, these stakeholders are building new relationships — often outside the four walls of the hospital. General Eco system relationship will be 5 relationships & interaction. Medical provider–payer relationship, medical provider– pharmacist collaboration, Medical device manufacture–clinician communication, employer/payer relationship, the consumer relationship across board.

[14] http://www.amcham.be/blog/2015/10/towards-innovative-healthcare-ecosystem

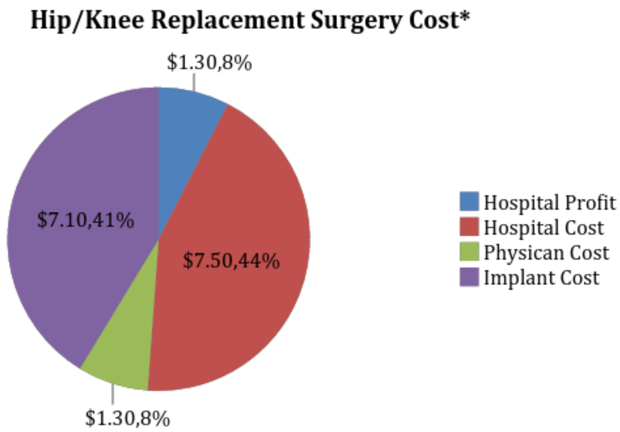


Figure 15. Hip and knee replacement surgery cost[15]

Orthopedics is characterized by a large value contribution by the manufacturers, surgeons, and finally hospitals for post implant services. As shown in Figure 7, the majority of 'primary activities' are completed by implant manufacturers while support activities are the responsibility of hospitals, private practices and surgeons. Clearly the largest value is created with the production of the device manufactures, then by surgeons or hospitals for the eventual implantation and surgery, and then by hospitals, doctor, or private practices for continued maintenance of the device. 3D printing could be potentially very disruptive to this model.

In the ecosystem, orthopedist will first string to communicate with patient. To treatment of patient, knee replacement will be one of option or final conclusive option among the treatment. So, doctors' recommendation will be most powerful influence rather than product's name value to patient. For this reason, the subsidy of orthopedist would be key market growing opportunity, and given populated to product quickly. As current those new technology (3D printing of knee replacement) adapted to doctors still be quite limited. In the Bay area, only less than 10 doctors can offer knee surgery with ConforMIS product, while conventional knee replacement can be offered more than 300 doctors included Stanford medical hospital.

[15] http://10156659.myku.tw/k/10156659/m/20151120205229.pdf

The outcomes of traditional implants mainly rely on the skills of surgeons who operate the surgery since they need lots of customizations per patient. However, 3D printing-based one moves this burden to device manufactures. This could be a threat to skilled surgeons while it could be an opportunity for fresh surgeons. From a different angle, it is an opportunity to the skilled surgeons as well because the operations for 3D printing-based approaches take less time than the traditional approaches which allows them to accommodate more patients.

As discussed in the previous section, the endurance of traditional implants is around 12-15 years. Misalignment, the common issue of traditional approach, causes pains after surgery and shortens the lifespan of implants. These days the average life expectancy of female in US is around 80 while some countries like Japan are approaching to 90. The old patients implant the first knees around their 60-70's and they highly likely undergo another surgery during their life time. 3D printing-based approach lasts 5-10 years longer than the traditional approach. This means that the implant is a once a lifetime event. The total out-of-pocket costs would be similar or even less. More than anything else, patients may not need to undergo the nightmare surgery any more.

Crossing the Chasm

ConforMIS unique technology by 3D printing has strong potential to growth in the market, which resolves current "off the shelf" product limitation. However, the current healthcare ecosystem with orthopedist has a gap to propagate services and products further, which needs to have more subside and encourage them to adopt.

Latest announced result from multiple clinical studies presented at the 2016 BASK (British association for surgery of the Knee). In one study, researchers at a leading academic institution compared the knee motion, or kinematics, of patients implanted with a ConforMIS iTotal® CR customized total knee replacement to patients implanted with an off-the-shelf Zimmer-Biomet NexGen® ("Legacy") or Persona® ("Modern") total knee replacement. The study demonstrated that ConforMIS iTotal patients exhibited assessed motion patterns more closely resembling a normal knee than patients with Legacy or Modern implants. Medical institution and doctor's recognition to build ecosystem are in progress, which will be critical for market growth for ConforMIS.

Horizon 3: 3D Printing in Bio-Medicine "The Pursuit of Probability"

Horizon 3 represents the emerging business landscape and futuristic view for 3D printing. The industry positively impacted and benefiting the most from 3D-printing is the Bio-Medical space.

Imagine there existed a capability to scan, custom 3D print and adorn facial human tissues, what if we were able to 3D custom print our own organs (Figure 16). This sounds un-realistic, but is indeed a possibility. The vision today can be a reality tomorrow.

In this new era of bio-medicine, the 3D printing machines we build are enabling to build bits and pieces of us. The potential is huge and out of this world.

Figure 16: Illustrating scanning and making copies of individual tissues for cosmetics and sale of printed organs. Inlay text shows number of people waiting for kidney and liver transplants in US (source: lnkd.org)

The bio-medical 3D printing space is currently at a tipping point. During the last decade, interest in the bio-medical space has spiked in orders of magnitude both from an investment and scientific research perspective. Key factors driving the trend are sophisticated printers, advances in regenerative medicine, and refined CAD software.

In the last few decades, 3-D printing has grown from a niche manufacturing process to a billion dollar industry (fabrication of toys, parts for airplanes, food). Scientists are applying similar 3-D–printing technology to print with living cells and create living tissues setting the foundation to create living organs one day. However, it should be noted that 3D-printing of tissues (using living cells) is much different and more complex than printing of plastics and metals.

The Art of 3D Bio-Printing

3D bio-printing is the process of creating cell patterns in a confined space using 3D printing technologies, where cell function and viability are preserved within the printed construct. Typically, it utilizes the layer-by-layer method to create tissue-like structures that can be used for drug discovery and medical research.

Magic behind the bioprinting Concept

The natural properties of cells are the magic behind the bioprinting concept. When placed in close proximity, cells aggregate and form their own extracellular matrix. This natural process finalizes the tissue from the printed cell.

Three steps involved in 3D bio-printing *(Source – Wikipedia).*

Pre-bioprinting - this process involves creating a printable model and choosing the materials that will be used. The common technologies used for bioprinting are computed tomography (CT) and magnetic resonance imaging (MRI). Post-tomographic reconstruction (layer-by-layer format), the now-2D images are then sent to the printer. Once the image is created, certain cells are isolated and multiplied. These cells are then mixed with a special liquefied material that provides oxygen and other nutrients to keep them alive.

Bioprinting – during this step, the liquid mixture of cells and nutrients are placed in a printer cartridge and structured using the patients' medical scans. When a bio-printed pre-tissue is transferred to an incubator, this cell-based pre-tissue matures into a tissue. Some of the methods that are used for 3D bioprinting of cells are photolithography, magnetic bioprinting, stereo-lithography, and direct cell extrusion.

Post-bioprinting – this process is necessary to create a stable structure from the biological material and needs to be well-maintained. This is accomplished by using mechanical and chemical stimulations (bioreactor technologies) that send signals to the cells to control the remodeling and growth of tissues.

Illustration of 3D tissue printing can be seen from Figure 17.

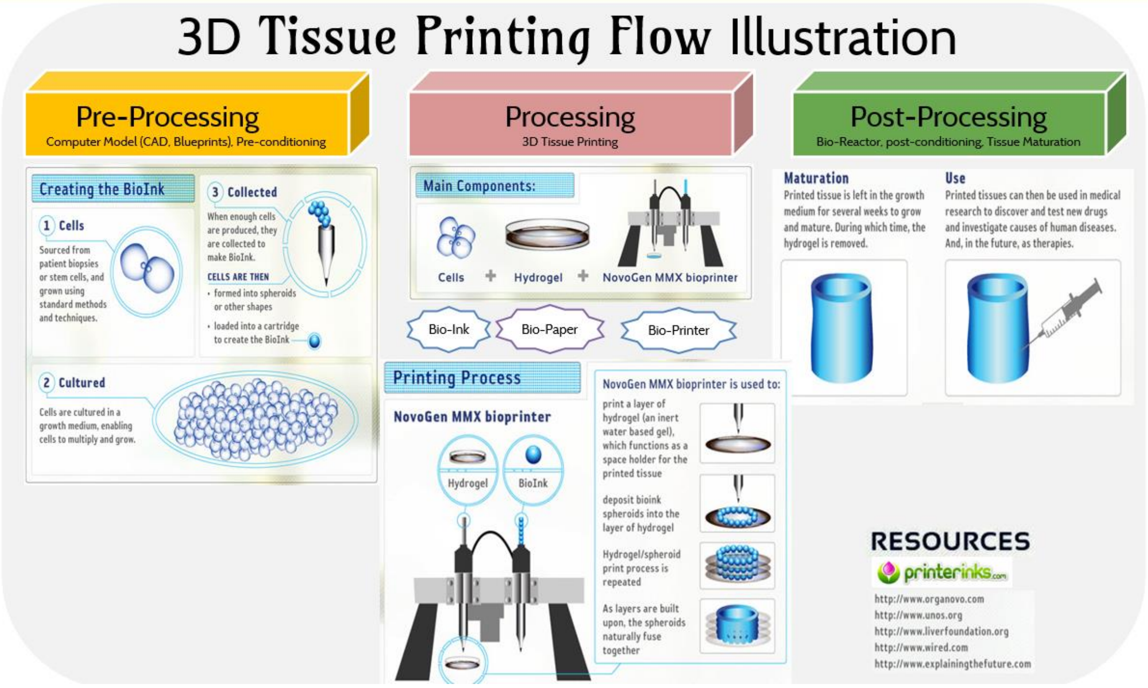


Figure 17: 3D printing process illustration covering the pre-processing, processing and post-processing steps. (Credit: organavo.com)

Potential of Bio-Printing

3D bio-printing has the potential to disrupt and revolutionize medical industry. This game-changing technology upon maturity, can eventually address the challenges we currently face in the area of drug discovery and organ transplantation (Figure 18).

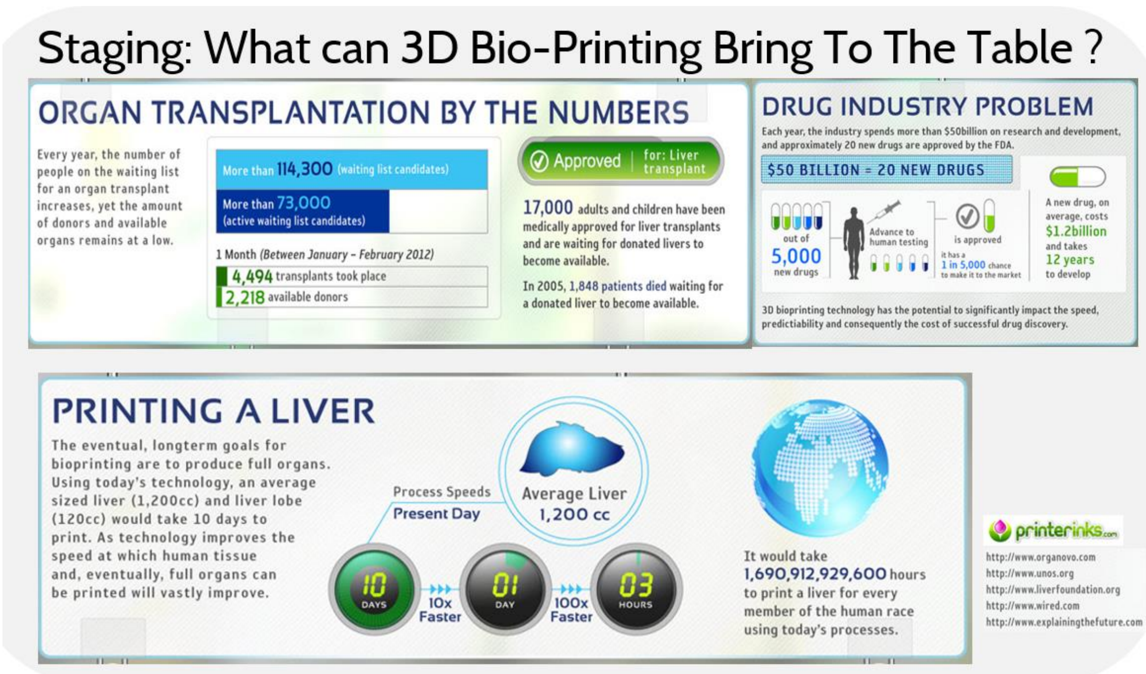


Figure 18: Potential applications of 3D bioprinting in drug industry and organ transplants. Illustrates the amount of time it takes currently to 3D print a human liver and the need to speed it up.

Organovo at a Glance

Human tissue and organ generation by bio-printing, a “Star Trek-like technology” isn’t developed overnight. A pioneer and leader in this magical space is “ORGANOVO” (Figure 19), who has just about the closest thing to it at the moment.

Figure 19: Illustrating the core competencies, scope, opportunities and challenges. *Source - http://www.fool.com/investing/general/2016/03/19/3-ways-technology-is-set-to-change-the-face-of-hea.aspx*

Core Competency

❖ **Organovo** is an early commercial stage publicly traded company focused on developing and commercializing functional human tissues using its proprietary 3D bio-printing technology.

❖ 3D human tissues are used in drug discovery, biological research, and as therapeutic implants for the treatment of damaged or degenerating tissues and organs.

Core Platform Technology

❖ Centered on multiple 3D bioprinting technologies, utilizing their proprietary NovoGen Bioprinters® platform.

- 3D bioprinting technologies enable a wide array of tissue compositions and architectures to be created, using purely cellular 'bio-ink' (building blocks comprised of only living cells), biocompatible hydrogels, or combinations of the two.

Company Vision

- Intend to introduce a paradigm shift in the generation of 3D human tissues
- Intend to leverage their unique 3D human tissue models to improve the current industry standard cell-based and animal model testing approaches
- Believe their foundational approach to the 3D printing of living tissues provides them with the opportunity to fill many critical gaps in commercially available preclinical human tissue modeling and tissue transplantation.

Competitive Edge

- Complex human tissue constructs created with 3D printing mimic native human tissue composition, architecture, and function. As an example - for toxicology, 95% of market uses liver cells in 2D, drawback is that it may not fully function like a liver, 3D allows replication of liver structure.

  (Source - http://www.outsourcing-pharma.com/Preclinical-Research/Organovo-on-track-for-3D-bio-printed-kidney-tissue-model)

- Replicating such a process is easier said than done due to Organovo's fully cellular approach (where no artificial scaffolds are being used) and intellectual property. Organovo's patent from Clemson University provides rights to use inkjet printer technology to dispense cells, and to create matrices of bio printed cells on agarose hydrogel materials.

Key Products & Sources of Revenue

- exVive3D tissue system – launched Nov 2015 – human liver cells formed into bio-ink, 3D printed into models offered to drug developers for toxicology and other pre-clinical studies

- ❖ 3D bio-printed kidney tissues – launched Sept 2016 (ability to study kidney function in an in vitro model)
- ❖ Leverage NovoGen MMX BioprinterTM a novel HW and SW platform for 3D cell culture in drug discovery application
- ❖ Revenues also derived from research service agreements, product sales, collaborative research agreements, and grants from the National Institutes of Health (“NIH”), U.S. Treasury Department and private not-for-profit organizations

Source – Organovo Holdings Form-10K, organovo.com

Ecosystem Analysis

“Organovo” is a story of great expectations in a typical “hype cycle”, with a great potential to revolutionize and disrupt the Bio-medical space. At this time, it is trying to define its foot-hold (Figure 20 shows how the stock price has performed over the horizon).

Figure 20: Illustrating the Horizon landscape of Organavo and stock performance over last few years.

Eco-System snapshot illustrated in Figure 21 shows great business potential through sound supply chain, research collaborations and partnerships. Focus on revenue sustainability, customers are the key for success.

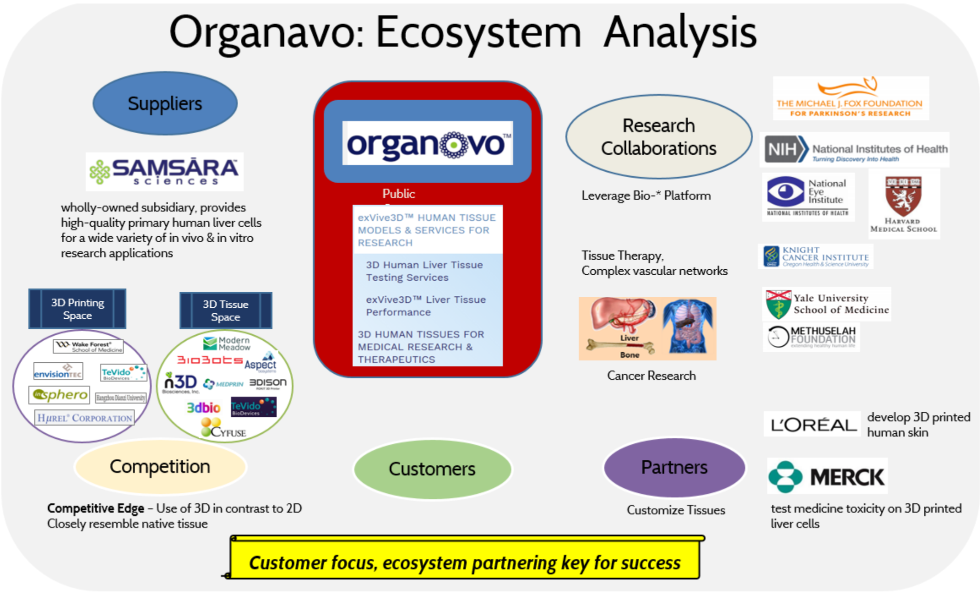


Figure 21: ecosystem illustration for Organavo covering suppliers, competitors, customers, research collaborators and partners.

Supply Chain (Human Cells)

- Purchase human cells from selected suppliers based on quality assurance, cost, effectiveness and constraints resulting from regulatory requirements

- Organovo established a wholly-owned subsidiary, Samsara Sciences, Inc. ("Samsara") for the purpose of providing high-quality primary human liver cells. Samsara provides human liver cells beyond Organovo's requirements to life science customers through typical commercial channels.

Partnerships

- L'Oréal (use of exVive3D Liver system) - develop 3D printed human skin it can test make up and beauty products

- Merck - test medicine toxicity on 3D printed liver cells, which is a key stumbling block today for getting new drugs to patients quickly

- Engaged in a number of early stage preclinical studies for a number of tissues expected to get into trials.

Research Collaborations

- Organovo currently has research collaborations with pharmaceutical, biotechnology and cosmetic companies, academic and research institutions and government agencies.

- These collaborations are focused on a variety of research projects, including: developing tissue-based drug discovery assays and tissues, developing more clinically predictive *in vitro* three-dimensional cancer models, exploring the use of our 3D liver tissues in toxicology, and exploring the use of 3D skin for testing skin care products.

Competition

- 3D bioprinting is an overcrowded Market. Organovo is just one of many (~30 plus companies) in the list of Commercial Developers of In-Vitro Models and Applications.

Opportunity

- While the analysis expectations for profits are not high until sometime in 2019, the magnitude of what Organovo is trying to do is appealing

- Estimates are that their current planned areas of research could lead to $400+ in annual revenue in the long run

- Possibility of a $1 billion+ buyout offer in the long run if any hint of a successful product is arrived at either through these partnerships or their own R&D (even if the company is not yet profitable)

Source-http://3dprintingventures.com/3d-printing-stocks-and-what-is-hapening-with-3d-printing-firm-organovo/

Game Changing Technology: Similarity to E-INK

Organovo (producer of “Bio-Ink”), has very close similarities with E-Ink. Both companies offer game-changing technologies with tremendous opportunity and potential in several markets (Figure 22).

Figure 22: E-ink and Bio-ink similarities

Lessons from the E-Ink Case

E-Ink, a start-up with leading edge technology – a special form of ink that could be used for electronic displays, which could potentially eliminate the need for paper. The company grappled with the issues of business model and focus. With a broader vision of being a sub-assembly (such as display modules) and end-product provided (such as eBooks), it eventually ended up just being a licensing material provider company.

Source – E-Ink in 2005, President and fellows of Harvard College

At this juncture, Organovo has very close resemblance with E-Ink with respect to the opportunities at hand, would it mean that Organovo should pivot, re-look at the opportunities at hand, and create a market for consistent growing revenue for sustainability?

Outlook and Opportunities for 3D-BioPrinting

As discussed so far, the commercial focus of 3D bioprinting today is primarily in developing small scale tissues for use with drug discovery and toxicity testing. The forecast is to use it to develop small pieces of organs such as skin, ears etc in the next few years and full fledged organs such as kidneys, heart, lungs etc in the farther future.

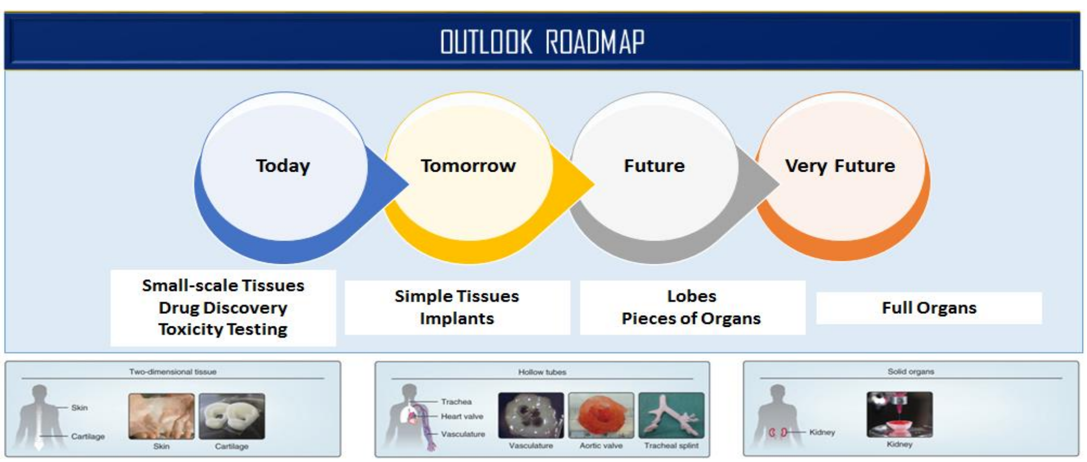


Figure 23: Short term and long term roadmap for 3D bioprinting market opportunities.

The main challenges in getting there are FDA approvals, acceptance and the ethical challenges that inevitably come up with such a technology. Sample ethical questions include people (esp criminals) changing their appearance and fingerprinting by grafting new skin; what a correct identification then is for a person etc. On the positive side, availability of bioprinting will greatly reduce clinical experiments on animals and potentially trafficking that may be happening today for organ transplants.

Figure 24: Challenges ahead for 3D bioprinting

The chart below shows the different challenges for 3D-bioprinting and their evolution over time. A primary challenge currently is the 3D-printer cost and throughput. For example, 3D-printing one human kidney today costs around $100K-$150K which is not very practical. This has been improving in the recent past with better technology, material and scale and is expected to be more affordable in the next few years. The CAD software needed for modeling these also needs work and is expected to take off in the next 5 years as the market grows.

	2013	2015	2020	2025
Challenges				
Material cost	Red	Yellow	Green	Green
Material selection	Red	Red	Yellow	Green
Printer cost	Yellow	Yellow	Green	Green
Throughput	Yellow	Yellow	Yellow	Yellow
Resolution	Green	Green	Green	Green
IP/ethical issues	Yellow	Red	Yellow	Yellow
Adequate design software	Yellow	Yellow	Yellow	Green
Opportunities				
Local manufacturing and reduced inventory	Red	Red	Yellow	Green
Cheaper and more accessible aftermarket parts and repairs	Red	Yellow	Green	Green
Novel material compositions and properties	Red	Red	Yellow	Yellow
Multifunctional structures	Red	Red	Red	Green
Increased premium on commodity materials	Green	Green	Green	Yellow
Customization	Red	Yellow	Yellow	Green

Table 5: Challenges and opportunities for 3D bio printing and how they will play out over time. (Credit: Anthony Vicari)

Conclusions: PUTTING IT ALL TOGETHER

We now summarize the overall findings, opportunities and challenges for the three horizons we looked at in 3D-printing for medicine. For each horizon, we also look at who they impact positively and who they disrupt negatively and the time horizon over which we expect this to happen.

In Horizon 1 of innovation, we looked at **Align Technology Inc**. which is a maker of Invisalign dental aligners, and is a well established leader in its market space. They have the first mover advantage and significant IP backing. They have substantial opportunities ahead -- primarily in terms of geographic expansion into other countries outside US. They can also create targeted solutions for specific demographics such as teenagers and other custom scanning needs within the dental space. They positively impact the customers who benefit from the invisalign solution and the orthodontists. Their customer satisfaction has been a key driver for them in the last 15-20 years since they got their FDA approval. A primary challenge we see for ALIGN Technology Inc. is the upcoming patent expiration in 2017 at which point they could be vulnerable to further competition -- especially from players with deep pockets such as 3M, HP and healthcare providers.

For Horizon 2, we looked at **ConforMIS Inc.** which provides a 3D printed knee replacement solution that is both customized and physiologically optimized for the patient. This customization to the patient's specific body makes their solution more comfortable and durable for the patient which is a big opportunity. This approach, being 3D printed on demand, also reduces inventory and opex for hospitals. So the key positively impacted group is the patients and hospitals. However, the main challenge we see for them is developing the ecosystem of doctors, patients and insurance companies so they are all suitable incentivized to participate in the disruption. We described some strategies for this using the money-side, subsidy-side analogy earlier and expect this disruption to take another 5 years or so to materialize.

For the longer Horizon 3, we looked at **Organavo Inc.**, which is one of the pioneers and creators of the bio-ink technology. They are still in an early stage with promising ground-breaking technology. The **sky is the limit** for their opportunities. They can print tissues for drug discovery in the near future and over time move on skin replacement and full scale organ replacement over time. This will be a tremendous value add for patients who will be benefitted by it -- especially think of war and accident zones where finding compatible organ replacements is a huge challenge now.

The industries that will be positively impacted by their growth will be the other bio-ink makers, CAD software makers, and the drug research companies as their research and development cycles can be shortened. The negatively disrupted industries will include areas such as kidney dialysis, diabetes and insulin operations, organ donation banks and logistics, pacemaker creators and other providers of stop gap treatments. However, we expect this to take another 5-10 years to materialize given the challenges we mentioned earlier about getting FDA approvals, wide spread acceptance and addressing concerns of ethics and costs.

On the while, the trends in 3D medical printing and bioprinting are positive and we expect that by 2025 or so the hype will materialize and we can have 3D-printed organ replacements customized for each person's need on demand.

Disruptive Company	**Positive Impact (who benefits)**	**Negative Impact (who suffers)**	**Impact Timeframe**	**WHY (and Threats)**
Align Technology ***Horizon 1***	Consumers; Orthodontists	Traditional Brce Suppliers	Growing since 1998 FDA approval	**Consumer Satisfaction ;** **Key IP-protection** **[IP expires in 2017]**
ConforMIS ***Horizon 2***	Patients, Hospital Inventory	Zimmer – established non-3D MKT leader	< 5yrs	**Ecosystem lagging**
Organovo ***Horizon 3***	Patients cured, War/accident areas, Organ transplants, Bio-ink makers, CAD software, Drug research	Kidney dialysis ops, Diabetes/insulin ops, Organ logistics/banks, Pacemakers Stop gap treatments	5- 10 yrs	**Approvals/Testing,** **Adoption,** **Ethics,** **Cost**

Table 6: Disruption summary for the three horizon cases on 3D medical printing.

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