Commentary

Reduced Supply in the Organ Donor Market and How 3D Printing Can Address This Shortage: A Critical Inquiry into the Collateral Effects of Driverless Cars

Patrick A. S. Mills [1] **and David K. Mills** [2,*]

1   OrganicNANO, Monroe, LA 71201, USA; patrick@precisionprocurementsolutions.com
2   Center for Biomedical Engineering and Rehabilitation Science, Louisiana Tech University,
     Ruston, LA 71272, USA
*   Correspondence: dkmills@latech.edu

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Abstract: Driverless cars, such as those currently operated by Uber and others as well as those being researched and developed by major and niche automobile manufacturers, are expected to dramatically reduce the number of highway fatalities in the coming years. While no one will fault any technology that safely and effectively protects and saves lives, many individuals with an array of medical conditions rely on organ donors to provide the liver, kidney, or other organs required to facilitate a life-saving organ transplant. Consequently, one collateral effect of the introduction of driverless car technology will be a reduction in the market supply of healthy organs for transplantation. In this paper, a venture capital lawyer, a medical researcher, and a bioengineer will establish the expected size of this reduction in supply, the associated harm resulting from this reduction, and discuss two promising technological solutions—bioprosthetics and 3D bioprinting of tissues and organs. In the case of both technologies, the authors will discuss the challenges and opportunities presented for institutional investors (private equity, venture capital, angel funds) and medical researchers in tackling the potential reduction in organ donations.

Keywords: autonomous vehicles; biorinting; organ donation; 3D printing

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1. Introduction

When "The Jetsons" debuted on ABC in 1962, Americans marveled at the various inventions that populated their world and dreamed of the technological wonders that the 21st century would bring. While such futurism undoubtedly inspired a generation of youngsters to become the engineers of tomorrow, the automotive industry has still not given consumers commercially viable flying cars. However, an invention perhaps as miraculous—driverless cars—are now beginning to roam the highways and byways of the United States and elsewhere, and industry estimates expect full adoption of driverless cars in the US by 2050 (Figure 1) [1].
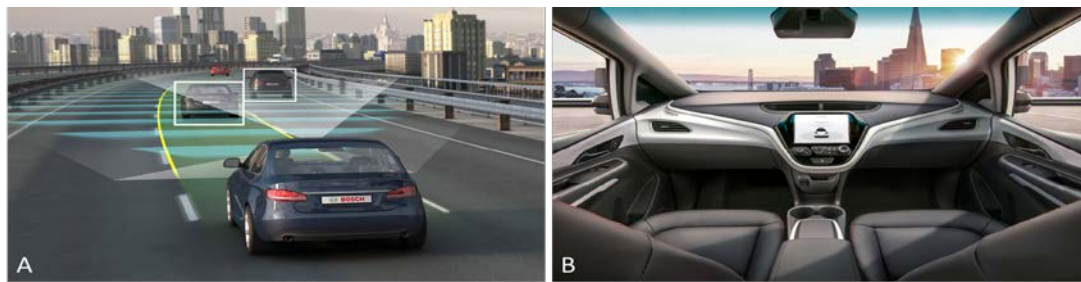
Figure 1. Artist's vision of autonomous driven car. (**A**) GPS, guidance systems and sensor networks are Integrated to provide a smooth and uneventful trip. (**B**) These cars will have the same comfort and features that current drivers are accustomed to having.

What is meant by "driverless or automated vehicles"? In May 2013, the National Highway Traffic Safety Administration (NHTSA) defined driverless or automated vehicles based on five levels of automation [2,3]. Level 0 vehicles possess no automated control systems, and Level 4 are fully automated vehicles. The intermediate levels based on driver assistance functions include Level 2 automation that involves at least two primary control functions designed to work in unison to release driver control over those functions and at Level 3. Automation enables the driver to cede full control of all safety-critical functions under certain traffic or environmental conditions. The vehicle monitors the driving conditions and situation for changes that require transition back to full driver control [3,4].

In contrast, in 2016, the Society of Automotive Engineers (SAE) recognized six different levels of driving automation from Level 0 to Level 5 [4]. Ordinary cars with no automated driving functions fall under Level 0, while a fully automated vehicle in which the dynamic driving task (DDT) is controlled by an automated driving system (ADS) entirely and without constraint is categorized as Level 5. At present, the industry standard in driving automation is almost entirely Level 1, in which stand-alone functions (such as automatic parking systems) assist human drivers, or Level 2, in which a combination of advanced functions performs part of the dynamic driving task [4]. In comparison, Levels 0 to 3 were remarkably similar. However, the SAE definitions subdivided the fully automated NHTSA Level 4 into SAE Level 4 and Level 5 [4]. The definitions above cover the complete range of vehicle automation, and automotive manufacturers are competing to advance beyond our current status (Level 2) and develop Level 3 or 4 technologies for the realization of full-fledged automated driving [3]. We will discuss this in more detail below. Driverless vehicles will be a significant driver of technological, biomedical, economic, and socio-political change, and the change will come much faster than most people expect. There will be a massive transfer of wealth to industries (and owners) who own the software, battery/power manufacturing, vehicle manufacture and servicing, and power generation and maintenance infrastructure [4,5]. Consolidation of industries, new regulatory and privacy concerns, new entrepreneurial opportunities, infrastructure changes, alteration in landscapes, and issues related to "high tech" hijacking are predicted consequences after the introduction of driverless vehicles [5,6]. It has been estimated that the impact of driverless cars, in terms of preventing lost time and productivity, is worth close to $50 billion USD to the tech industry [1]. However, the economic, medical, and social implication of driverless car technology suggests that this innovation does not come without a price tag. Many economic burdens will be removed; for example, human error is responsible for over 90% of automobile accidents [7]. A reduction in injuries from these accidents will eliminate the need for auto insurance policies, reduce demand for car repair and medical services, and make traffic police redundant [8,9].

One of the primary value propositions for driverless cars that employ ADS will be far fewer accidents than human drivers, saving a significant number of road fatalities each year [8,9]. However, these saved lives have a tradeoff: one of the primary sources of organ donation for patients requiring a transplant operation is victims of car accidents. Should driverless car technology successfully penetrate the automobile market and achieve adoption rates as predicted, then the consequent drop in car

accidents will result in a diminution of supply of organs for transplant. As it would be irrational to maintain the rate of accident fatalities in order to benefit transplant recipients, the question that healthcare providers, medical researchers, and medtech/biotech investors must ask is "what current or future technology is best positioned to resolve this decrease in the supply of organs"?

While other possible solutions certainly exist, this paper will consider the potential of current and future 3D printing technology to resolve the problem of a decreased organ supply resulting from the introduction of driverless cars. In general, there are four pillars to the value proposition of medical 3D printing. Medical 3D printing technology can be customizable, tunable, scalable, and patient-specific [10,11]. Customizable means that the technology can be highly customized to meet the needs of consumers—from institutional hospitals to private practice physicians to the direct-to-home consumer market. Tunable means that technology can be tuned at the molecular level to meet the needs of different applications or markets. Scalable means that the technology can be cost-effectively scaled to meet the demands of any customer base. Patient-specific means that technology can be tailored to patient-specific needs such a patient history, genetic makeup, age, or sex. Given the overarching strengths of 3D printing for healthcare applications, it stands to reason that current solutions such as 3D printing of tissues and organs offer promise in resolving the coming shortage of organs following the adoption of driverless cars [12,13].

This commentary seeks to address the collateral effects of the widespread adoption of driverless cars—specifically a reduction in the supply of organ donations—as well as advise investors and medical researchers on current and future technology that may resolve this issue. While many scholars have argued for or against the legalization of commercial organ sales as a way to alleviate the issues of transplant patients—scarcity, wait time, tissue matching, etc.—these scholars are missing a more obvious solution that does not violate the established ethics of any culture, nationality, or religion: scientific advancement. Through this paper, the authors seek to establish that current and future technology exists or will exist that can overcome the immense challenges posed by organ transplantation, especially in the face of an eventual decline in donors. Advance planning for this eventuality is a critical need.

This research question is vital to the wellbeing of transplant patients worldwide, their families, and their caregivers. Currently, almost 120,000 transplant operations take place worldwide every year [14,15]. However, in the United States, patients can wait three years or longer for a transplant operation. In Europe, over 40,000 patients suffer on dialysis who might lead happier and more productive lives almost instantaneously once medical science can reliably 3D print kidneys for implantation [16]. Advances in medical technology have the potential to drastically improve the quality of life for many the world over. In addition to humanitarian concerns, this inquiry is necessary because the primary alternative to the shortages and wait times that occur through legal transplantation is to turn to the black market and such means as "transplant tourism." While apocryphal stories such as the man who wakes up in his hotel room in a bathtub remain the stuff of urban legend, real-world commercialism drives a growing illegal organ trade that mostly preys on society's most vulnerable citizens. Currently, between 5–10% of all transplants take place via commercially acquired organs, and some countries supply thousands of kidneys and livers to foreign recipients via executed prisoners at a significant profit [15]. The price of a kidney or liver on the black market can exceed $150,000 USD in some markets [16]. With such illicit financial incentives, it is doubtless that a significant diminution in the supply of organ donors will foster greater criminal trafficking of organs.

There are also practical, economic matters that make this inquiry necessary. The need for transplant organs such as kidneys currently far outpaces the rate of growth in transplant operations. Currently, hemodialysis treatment costs $89,000 USD per year per patient in the United States [17]. By comparison, the cost of transplantation is only $32,000 USD with $25,000 USD in annual post-operative care [17]. This amounts to one-year savings of $32,000 USD and five-year savings of $288,000 USD per patient, and 35% of hemodialysis patients have a 5+ year survival rate [17]. The onset of driverless cars will, no doubt, present incredible economic and social opportunities during the first half of the 21st century.

However, these opportunities come at the price of a decrease in the number of legal organ donors and, with this, challenges that medical researchers and private investors must overcome to avoid a humanitarian crisis and uptick in global organized crime in human organs [18]. The shortage of donated organs has led to the development of the international organ trade, where potential recipients travel abroad to obtain organs through commercial transactions [19]. The international organ trade has been recognized by governments across the globe as a significant health policy issue in the international community [18,19]. According to the United Nations, organ trafficking (a form of human trafficking) falls into three categories: (1) traffickers who trick the victim into giving up an organ for no cost, (2) con artists who convince victims to sell their organs but who do not pay or who pay less than they agreed to pay, and (3) doctors who treat people for ailments that may or may not exist and remove the organs without the victim's knowledge [18]. One only has to search Craigslist to see the huge number of advertisements for organs. For example, an NBC Chicago investigative report documented that hundreds of Illinois citizens were willing to sell their kidney for up to $30,000 USD [20]. We will argue that 3D printing and bioprinting will be a powerful tool in resolving this problem and the worldwide shortage of human tissues and organs.

This paper begins by discussing the technology employed by driverless cars and how this will lead to a decrease in fatal accidents on global highways. Then, this paper discusses how this drop in fatal accidents will result in fewer organ donations as well as the absolute impact on organ donation. Finally, this paper considers current and future 3D printing technology, the viability of each technology for resolving issues with the supply of organs, and the opportunities and challenges presented by each technology. The paper concludes by providing recommendations regarding employment of human and financial capital for research and development of current and future 3D printing technology.

2. Driverless Car Technology and the Organ Donor Supply

### 2.1. Driverless Car Technology Explained

According to SAE International, the J3016 standard determines the level of automation primarily by the extent to which the human driver or the vehicle itself controls the dynamic driving task [4]. The dynamic driving task is defined as operational tasks such as steering and braking and tactical assessments such as determining when to signal, turn, or change lanes but not strategic decisions such as choosing a destination. Within the six-level standard, the crucial distinction occurs between Level 2 and Level 3. At Levels 2 or below, the human driver performs at least part of the dynamic driving task; at Levels 3 or above, the vehicle's automated driving system performs the entire dynamic driving task (Table 1).

Table 1. SAE International's levels of automation.

Level 0	**No Automation**—the human driver performs the entire dynamic driving task. This level includes vehicles with warning or intervention systems such as lane departure warning or braking assistance because this assistance is not sustained and, therefore, does not control the human driver's basic role. All traditional cars from the advent of the automobile until today, including most current vehicle models fall into this category.
Level 1	**Driver Assistance**—one or more *driving modes* exist that the human driver can engage that will execute certain aspects of steering or acceleration/deceleration by employing information about the driving environment via the utilization of a system of onboard sensors. Within this sort of vehicle, the human driver remains responsible for all driving tasks other than that performed by the vehicle's limited driving mode. Jaguar Land Rover's experimental Range Rover Sport that utilizes an off-road cruise control system is an example of a Level 1 autonomous vehicle.
Level 2	**Partial Automation**—one or more *driving modes* exist that the human driver can engage that will execute ALL aspects of BOTH steering and acceleration/deceleration by employing information about the driving environment. Within this system, the human driver is still required to monitor the driving environment—the tactical driving task—and to serve as a fallback performer (manual intervention). Some experts consider Tesla's Autopilot system to be a Level 2 autonomous driving system.
Level 3	**Conditional Automation**—one or more *driving modes* exist that perform all aspects of the dynamic driving task, including monitoring the driving environment. Like Level 2 automobiles, Level 3 automation systems still require the human driver to serve as a fallback performer should the system request manual intervention. Other experts consider Tesla's Autopilot system to be a Level 3 autonomous driving system.
Level 4	**High Automation**—one or more *driving modes* exist that perform all aspects of the dynamic driving task as well as providing fallback performance should the human driver fail to respond to a request to intervene. In other words, when a problem occurs, the car can resolve the issue without human assistance. The fleet of self-driving taxis currently being developed by Ford for release in the US market by 2021 qualify as Level 4 autonomous vehicles.
Level 5	**Full Automation**—ALL driving modes are fully automated meaning the vehicle maintains control over the dynamic driving task under all roadway and environmental conditions. Only strategic tasks such as picking a destination remain in the hands of the human driver or, in the case of a driverless taxi, the human passenger. The vehicle that Google is developing through its Waymo subsidiary is expected to utilize Level 5 automation.

At a more technical level, driverless cars function by utilizing a system of sensors that monitor the vehicle's surroundings to generate data, allowing the automated driving system to operate the vehicle amid other cars as well as varying road and weather conditions. More specifically, autonomous vehicles employ radar sensors to monitor the location of nearby vehicles. Video cameras are utilized to detect traffic lights, read road signs, and track vehicles, pedestrians, and obstacles. Lidar sensors assist with detection of road edges and lane markings by bouncing light pulses off the car's surroundings. Ultrasonic sensors are employed in the wheels to detect the location of curbs, vehicles, and other obstructions while parking. Controlling driverless cars mean more connectivity and will also allow more passenger freedom, permitting travelers to engage in other activities while leading to a reduction in auto accidents, especially those due to distraction and cellphone use (Figure 2).
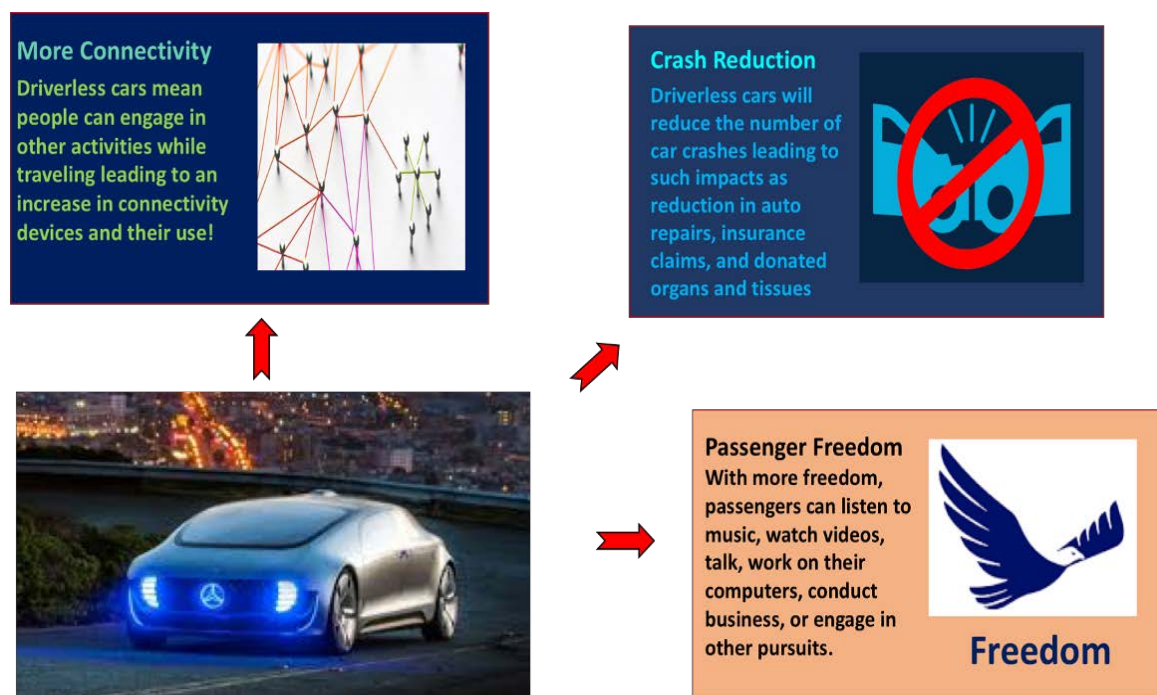
Figure 2. Adoption of autonomously driven vehicles proposes a reduction in traffic accidents, enhance connectivity for driver and passenger, and passenger freedom to pursue a range of family, leisure, and work activities.

2.2. The Current State of Driverless Car Technology

While the number of driverless cars on the road in 2016 number only in the thousands, that number is expected to grow to 10 million by 2020 [21]. Numerous companies have begun to develop self-driving car prototypes in both the traditional automotive space (Ford; GM; Mercedes) and the tech space (Google; Apple). Many more have already built prototypes that they are currently road testing in the United States, Europe, or Asia. These companies—specifically GM and Toyota—have also begun to lobby their local governments to revise highway laws to allow driverless cars on the road, paving the way for adoption by consumer and industrial users [22]. Controlling the system, a central computer analyses the information from the vehicles numerous sets of sensors in order to steer, accelerate, and brake the automobile.

Perhaps the best-known driverless car technology, Google's prototype, has been roadworthy since 2011 and is under development through the wholly owned subsidiary Waymo. While development timelines have stalled somewhat recently, Google is pursuing corporate partnerships with Honda and others through which to introduce its autonomous car technology [23]. They currently have at least 160 vehicles on the road [24]. GM is currently working through its Cruise Automation subsidiary to place thousands of driverless cars on the road in 2018 in partnership with Lyft—a major ride sharing company [24]. Ford is currently developing a prototype Fusion with plans to place a fully autonomous model on roads by 2021 [25]. They will triple their autonomous car fleet to 90 in 2017 [24]. Ride sharing leader Uber already has a number of driverless cars on the road in the United States and has developed a self-driving semi-truck that successfully delivered a load of 50,000 cans of Budweiser [26]. However, Uber cars have also already been involved in on-road accidents, leading to increased scrutiny by regulators [27]. In addition to the above cases, Jaguar, BMW, Tesla, Airbus, and a number of other companies both large and small are also developing and testing driverless vehicles on the highways and byways of major metropolitan areas [28–31]. Alphabet and the State of Michigan have recently entered into a collaboration designed to aid in developing infrastructure for self-driving cars as well as autonomous buses and shuttles. Michigan will dedicate a busy stretch of the interstate between Detroit and Ann Arbor into a self-driving car and connected corridor.

Many recent failures of autonomous cars and the injuries and death of drives has raised a noticeable degree of concern among the public (Figure 3). Failures in navigation and road stability driving stability are major industry concerns. Action must be taken to resolve issues such as software failures, security against hackers, and the potential for sensor malfunction. There are several possible solutions to mitigate problems with ADC technology. One solution is the use of special lane markings and road signs with hidden functionality that will direct autonomous cars, ensuring higher levels of safety and greater reliability.
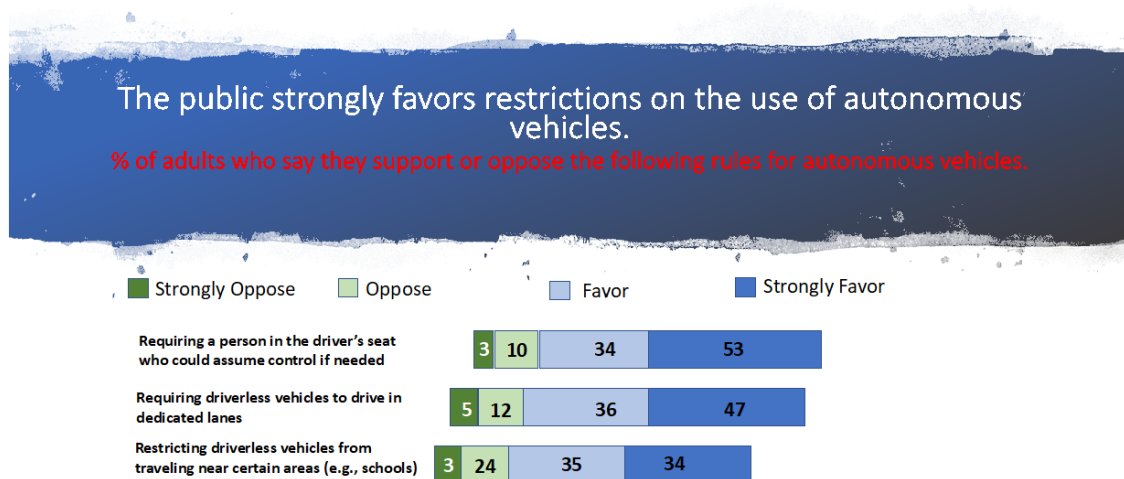
Figure 3. Public concern with autonomous vehicles remains an industry concern. Figure adapted from https://www.pewresearch.org/internet/2017/10/04/automation-in-everyday-life/.

One example is 3M's Connected Roads project. This project is focused on retrofitting existing road marking technologies to assist autonomous cars with enhanced navigation on existing roads. 3M smart has specifically designed codes that the vehicle would use in linking back to a central database for regularly updated road and weather information. These smart codes are currently being tested and developed by 3M in cooperation with several governmental agencies. PPG Industries has taken a different approach to ensure road safety. PPE is developing paints and related coatings that improves vehicle visibility to radar and light detection and ranging (LIDAR) sensors used in autonomous driving systems. Enhanced LIDAR vehicle designed coatings detection are being tested that promise improved visibility and reliability for dark colors or in challenging environmental conditions. Still, sensor and software security, just like with the cars themselves, will continue to be a concern.

2.3. Expected Dilution of Supply Following Introduction of Driverless Cars

In 2008, 100,800 solid organ transplants occurred worldwide according to WHO data on 104 countries comprising 90% of global population—69,400 kidney transplants; 20,200 liver transplants; 5400 heart transplants; 3400 lung transplants; and 2400 pancreas transplants [32,33]. As of 2015, that number stood at 126,670 organ transplantations worldwide [34]. At that rate of growth—2.3% per annum—280,672 transplants will occur worldwide in the year 2050. However, in the United States alone, the need for donor kidneys is rising at a rate of 8% per year [35]. As the world's population ages and medical technology offers longer lives to a greater percentage of the global population, the increased need for transplant donors will stretch the resources of market supply to the breaking point. The impact of driverless cars may be that breaking point.

The full adoption of driverless cars by 2050 is expected to reduce the number of highway accidents by as much as 90%. Currently, 15–20% of organ donations come from highway fatalities. At this rate, the adoption of driverless cars would result in a decline of 14–18% in the supply of organs for transplant in the United States. The chart below considers the impact at various rates of adoption (Table 2).

Table 2. Estimated decline in the supply of organs for transplant in the United States.

% Car Accidents.	25% Adoption	50% Adoption	75% Adoption	90% Adoption
12.5%	−3.125%	−6.25%	−9.375%	−11.25%
15%	−3.75%	−7.5%	−11.25%	−13.5%
17.5%	−4.375%	−8.75%	−13.125%	−15.75%
20%	−5%	−10%	−15%	−18%

DIMINUTION in KIDNEYS [1] (Based on WHO data for 2015 in United States).

% Car Accidents	25% Adoption	50% Adoption	75% Adoption	90% Adoption
12.5%	−811	−1621	−2432	−2918
15%	−973	−1945	−2918	−3502
17.5%	−1135	−2270	−3404	−4085
20%	−1297	−2594	−3891	−4669

DIMINUTION in LIVERS (Based on WHO data for 2015 in United States).

% Car Accidents	25% Adoption	50% Adoption	75% Adoption	90% Adoption
12.5%	−212	−423	−635	−761
15%	−254	−508	−761	−914
17.5%	−296	−592	−888	−1066
20%	−338	−677	−1015	−1218

DIMINUTION in HEARTS (Based on WHO data for 2015 in United States).

% Car Accidents	25% Adoption	50% Adoption	75% Adoption	90% Adoption
12.5%	−88	−176	−264	−317
15%	−106	−211	−317	−381
17.5%	−123	−247	−370	−444
20%	−141	−282	−423	−507

DIMINUTION in LUNGS (Based on WHO data for 2015 in United States).

% Car Accidents	25% Adoption	50% Adoption	75% Adoption	90% Adoption
12.5%	−65	−130	−194	−233
15%	−78	−155	−233	−280
17.5%	−91	−181	−272	−326
20%	−104	−207	−311	−373

DIMINUTION in PANCREAS (Based on WHO data for 2015 in United States).

% Car Accidents	25% Adoption	50% Adoption	75% Adoption	90% Adoption
12.5%	−30	−59	−89	−107
15%	−36	−71	−107	−128
17.5%	−41	−83	−124	−149
20%	−47	−95	−142	−170

[1] Assumes each deceased donor donates both kidneys.

Beyond the loss of donors, every patient that must continue to wait for a transplant entails further cost for medical care while waiting for an organ transplant. Below is a three-year chart of cumulative hemodialysis costs for patients based on the diminution of kidney donors given the average current wait time of 3.6 years (Table 3) [36].

When reviewing these numbers, also consider that a 2016 hemodialysis cost of $89,000 USD will equal $261,433 USD in 2050 dollars based on the 3.22% historic average rate of inflation [33]. This is 2.93 times greater or nearly a tripling of prices. Further, consider that at the current rate of 8% yearly increase in need for kidney transplant versus 2.3% increase in transplant operations that the likely overall cost to the global health care system will be significantly larger than these numbers currently can project. Also, bear in mind that 80% of all hemodialysis costs are currently paid for by the already severely stretched MEDICARE system. Currently, the cost to MEDICARE is $32 billion USD; factoring in inflation and the rising number of end stage renal disease (ESRD) patients in 2050, that cost in the United States will likely rise to several hundred billion dollars [33,35].

Table 3. Estimated three-year hemodialysis cost impact analysis after adoption of autonomous vehicles.

ONE					YEAR CHART
Medical Costs	**25% Adoption**	**50% Adoption**	**75% Adoption**	**90% Adoption**	
12.5%	$72,140,063	$144,280,125	$216,420,188	$259,704,225	
15%	$86,568,075	$173,136,150	$259,704,225	$311,645,070	**YEAR CHART**
17.5%	$100,996,088	$201,992,175	$302,988,263	$363,585,915	
20%	$115,424,100	$230,848,200	$346,272,300	$415,526,760	
TWO					
Medical Costs	**25% Adoption**	**50% Adoption**	**75% Adoption**	**90% Adoption**	
12.5%	$216,420,187	$432,840,375	$649,260,562	$779,112,675	
15%	$259,704,225	$519,408,450	$779,112,675	$934,935,210	**YEAR CHART**
17.5%	$302,988,262	$605,976,525	$908,964,787	$1,090,757,745	
20%	$346,272,300	$692,544,600	$1,038,816,900	$1,246,580,280	
THREE					
Medical Costs	**25% Adoption**	**50% Adoption**	**75% Adoption**	**90% Adoption**	
12.5%	$432,840,375	$865,680,750	$1,298,521,125	$1,558,225,350	
15%	$519,408,450	$1,038,816,900	$1,558,225,350	$1,869,870,420	
17.5%	$605,976,525	$1,211,953,050	$1,817,929,575	$2,181,515,490	
20%	$692,544,600	$1,385,089,200	$2,077,633,800	$2,493,160,560	

3. Bioartificial Organs as a Solution to Organ Failure

3.1. Overview of Bioartificial Organ Technology

In general, a bioartificial organ advances current extracorporeal biomedical device technology to incorporate an intracorporeal device. In other words, a biomedical device that utilizes some synthetic and some organic components is assembled that can be medically inserted into the human body to replace the function of a deficient or failed organ [37]. Researchers in this area either do or will utilize MEMS (microelectromechanical systems) and nanotechnology engineering to produce a device that is small enough to be cost effective, scalable, and easily inserted into a human patient [38,39].

Tissue or organ replacement due to aging, diseases, accidents, and birth defects is a critical medical problem [39]. Current treatment for organ failure relies mostly on organ transplants from living or deceased donors [5]. However, there is a chronic shortage of human organs available for transplant [5,34]. In 2009, 154,324 patients in the USA were waiting for an organ [10]. Only 27,996 of them (18%) received an organ transplant, and 8863 (25 per day) died while on the waiting list [40]. As of early 2014, approximately 120,000 people in the US were awaiting an organ transplant [41]. Organ transplant surgery and follow-up is also expensive, costing more than $300 billion USD in 2012. [40]. An additional problem is that organ transplantation involves the difficult task of finding a donor who is a tissue match. This problem could likely be eliminated by using cells taken from the organ transplant patient's own body to build a replacement organ [42,43]. This would minimize the risk of tissue rejection, as well as the need to take lifelong immunosuppressants [42,43].

3.2. Current State of Bioartificial Organ Technology

A number of bioartificial organ technologies already exist and are in use in human patients. Bioartificial livers (BALs) have existed since 2001, when Dr. Kenneth Matsumara developed a device that *Time* named its invention of the year [39]. Since that time, BAL technology has improved dramatically, and many cases of acute liver failure are currently treated with BALs. However, the present state of technology functions only as a bridge treatment, allowing patients with diseased livers to wait out a transplant or for their liver to heal naturally [42].

Many institutions are currently researching a bioartificial pancreas; however, no such device is presently available for patients. Significant progress has been made in mimicking the function of a

healthy pancreas, and the Imperial College London is currently conducting ambulatory trials of their bio-inspired artificial pancreas with type-1 diabetes patients [43]. The state of technology is much the same with bioartificial kidneys: while no viable device currently exists, many lines of research are closing in on a workable—and marketable—solution. At present, the FDA is working closely with the Kidney Project—a joint initiative between UC-San Francisco and Vanderbilt University—to bring the first bioartificial kidney to market. The development team expects to enter human clinical trials as soon as later in 2017 [43].

As of 2017, no functional bioartificial heart exists, although wholly synthetic, artificial hearts have existed since 1982. In 2008, scientists created the first bioartificial hearts from rat cadavers. In 2014, researchers developed human-sized bioartificial porcine hearts. Currently, however, researchers have yet to develop a transplantable, bioartificial heart utilizing either porcine or human cadaver hearts [44].

4. Bioprinting as a Solution to Organ Failure

4.1. Current State of Bioprinting Technology

Tissues in the body differ significantly in cellularity, composition and character, and metabolism. Distinct subpopulations of cells secrete signaling molecules, such as growth factors and other cytokines, that aid in maintaining cell viability and function (Figure 4). Over the past decade, three-dimension (3D) bioprinting as an emerging new technology for tissue engineering has made significant progress towards the regeneration of replacement tissues [45–47]. 3D bioprinting is complicated as there are critical design considerations such as choice of materials, cell type(s), mitogenic and differentiation factors, and other technical challenges [48–52]. In bioprinting, various biofabrication methods to construct a tissue or organ from a patient's cells or stem cells, including inkjet printing [53–55], bioextrusion or robocasting [56–58], laser-based printing [59–61], and selective laser sintering [62,63], have been developed for the 3D printing of live cells and bioscaffolds. Each of these bioprinters has unique methods for fabricating 3D cell structures with excellent resolution and viability and employing a variety of bioinks [50,51].

Advances in 3D printing have also enabled the assembly of cells, extracellular matrix and polymeric materials to form in vitro cellular models for the study of disease pathogenesis, drug efficacy studies, and new drug discovery [48]. Three-dimensional bioprinting methods, in particular, have made it possible to precisely control the cellular microenvironment architecture and produce the desired design characteristics to produce the desired cellular behavior [47,48].

Stereolithography-based 3D bioprinting, for example, is one of the most popularly used technologies in tissue construct fabrication [49]. This 3D printing technique can create matrices with suitable mechanical strength in configurations that can spatially support multiple cell types. This method of bioprinting has enabled the fabrication of bone, cartilage, and skin [50]. Robocasting, another bioprinting method, has been used to produce may objects (in particular, ceramics) by extruding a filament of paste (known as an "ink") through a fine nozzle, and the construct is built layer-by-layer according to a computer aided design (CAD) model [51,52]. The properties and composition of the ink are considered to be the most important factors in robocasting, and considerable research effort has been directed towards the development of novel bioinks [53]. The key challenge has been developing an optimal method for printing viable cells with high survival rate and producing strong cell-seeded scaffolds simultaneously. The other key design consideration is the inclusion of bioactive factors (drugs, growth factors, DNA, and metal nanoparticles) that stimulate or direct cellular behavior [54].
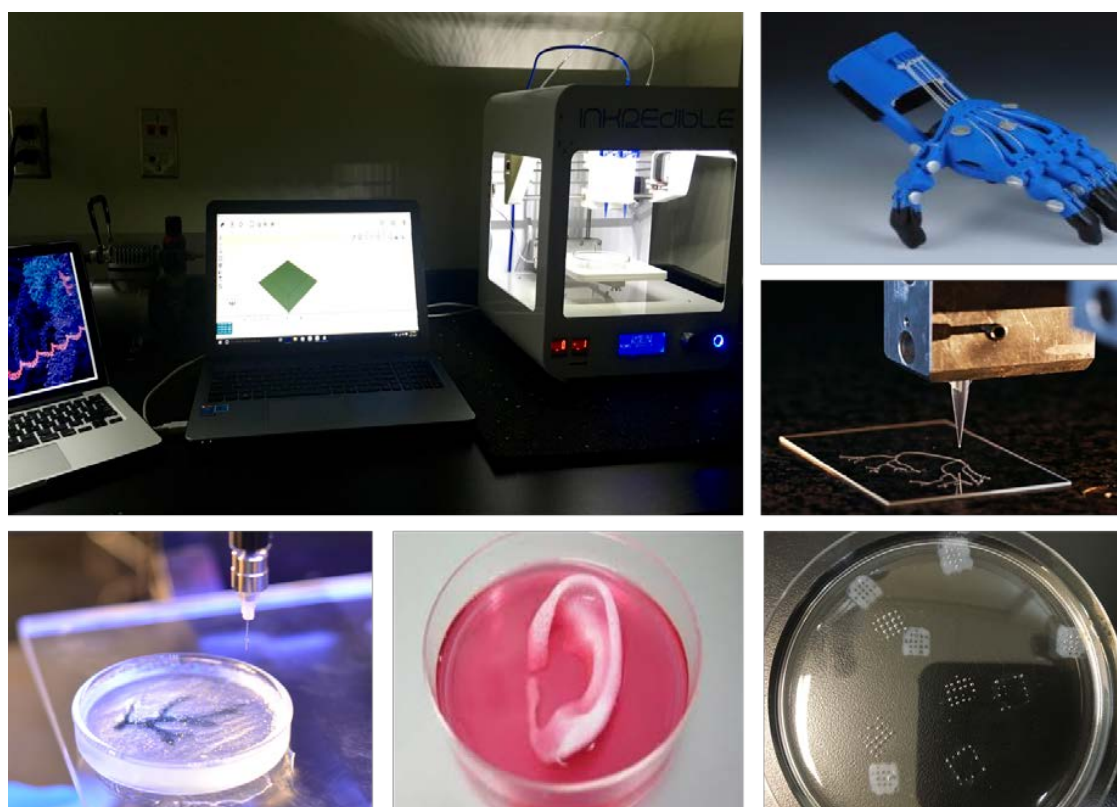
Figure 4. Bioprinting uses computer-aided design, bioinks, and a bioprinter to produce tissues and organs (**top left**). Three-dimensional printed prosthetics using thermoplastics will remain an essential clinical tool (**top right**). Examples of bioprinted tissues and organs include ducts (**top middle**), blood vessels (**lower left**), an external ear (**lower middle**), and bone implants (**lower right**).

4.2. Opportunities Presented by Bioprinting

According to Grand View Research, is expected to reach $4.1 billion USD by 2026 registering a compound annual growth rate (CAGR) of 19.5% [55]. More specifically, this growth will be keyed by the need for donor kidneys due to diseases such as chronic kidney disease (CKD). Dental segments, prosthetics, and 3D-printed medical devices (syringes, catheters) are seeing the greatest growth [55]. Given a rapidly aging world population with a rapidly growing global middle class that can afford and will demand cutting-edge healthcare, it is highly likely that the market for bioprinted organs—and bioprinting in general—will see steady growth throughout the first half of the 21st century [52,53]. Venture capitalists poured $10.6 billion USD into healthcare startups in the first half of 2018 [56]. This sustained market growth provides an ample opportunity for institutional investors with the patience to invest in healthcare and biotechnology startups [56]. "The risks may be high and returns may take longer, but as Swiss philosopher Jean-Jacques Rousseau said: although patience is bitter, its fruit is sweet" [56]. Additionally, of course, such investment will also pay dividends on the humanitarian side of the equation.

The first bioinks were used in drop-on-demand cell printing were simple salt solutions [57,58]. Bioinks are usually a biopolymer gel used as a carrier for embedded cells and also provide a protective environment [58]. Bioinks, as a carrier, are then used in a variety of bioprinting technologies including robocasting, ink jet, direct ink writing, and stereolithography [59]. Examples of bioinks include agarose, alginate and chitosan-based bioinks, cellulose, collagen, fibrin, hyaluronic acid, and silk. Synthetic biomaterial that are often used include gellan gum, gelatin methacrylate pluronic, and polyethylene glycol [60].

The future of bioprinting resides in integrated bioprinters. Dr. Anthony Atala recently introduced a tissue-organ printer (ITOP), a device that prints cells within a hydrogel supported by a temporary scaffold [61]. This printer can produce human-sized tissues containing microchannels that aid in oxygen and nutrient transport throughout the construct. Cheng et al. (2020) recently developed a handheld 3D printer that applied a stem-cell-loaded bioink directly onto a wound, such as burns, to promote tissue healing [62].

Three-dimensional bioprinting has the capacity to produce transformative results for patients suffering from numerous health conditions not just organ failure [64]. In addition to lives saved and lives improved, 3D bioprinting also has the capacity to drive significant medical cost savings in the United States and worldwide. Additionally, the prices of medical procedures and biomedicines could see a drastic cut in cost if competition accelerates due to 3D printing. In addition to reducing costs, 3D printers may also simplify treatment reduce inherent inefficiencies. Due to 3D bioprinting's humanitarian and financial benefits for human society, it will likely be one of the most important medical innovations of this generation.

Short-term applications that have seen the greatest impact relate to drug testing (thereby reducing the need for animal testing), as drug testing can take place on "organ-on-a-chip" technologies [62]. A patients' own stem cells can be used to generate bioprinted organoids that test the potency and efficacy of pharmaceutical drugs [64]. This will eliminate the use of animals for drug testing, and more efficient and reliable results will ensue, as the testing can be done on human tissues [64]. Indeed, there is the further potential for personalized medicine, where a particular individual's reaction to a drug can be gauged, alleviating the incidence of adverse drug reactions, and dosages can be adjusted to suit the required efficacy [65].

4.3. Commercial Challenges of Organ Replacement Technology

Three-dimensional bioprinting of human tissues and organs—or of anything else for use in medicine and healthcare—share many of the same challenges that any new biomedical or biotechnical advancement faces in penetrating the marketplace. First and foremost, researchers—whether in public institutions or private corporations—must develop the technology to the point where regulators such as the Food and Drug Administration (FDA) in the United States or the European Medicines Agency in the European Union will approve products for market. In the case of a bioprinted organ, this regulatory process will be especially burdensome, as this particular technological use case consists of a life-or-death scenario for most if not all consumers. Once regulators are appeased, researchers must convince clinical partners to adopt their products so bioprinted organs can become widely disseminated and gain traction in the marketplace.

Finally, researchers must work hand-in-hand with clinicians to promote their solution to would-be patients who may be leery of a new and untested innovation compared to waiting their turn on a donor list. Furthermore, they must accomplish all of this while balancing the concerns of investors, managers, and administrators. While not an impossible series of tasks to complete, the opportunity—and inherent investor patience—is not the same as for other industries with more robust, forecasted growth such as artificial intelligence.

5. Legal Challenges of Organ Replacement Technology

There are two primary legal risks related to commercializing a 3D-printed human organ: products liability and patentability. The case of products liability is well understood. Any time a manufacturer produces a medical device for implantation in the human body, they run the risk of a legally identifiable defect resulting in rejection or complications that accrue tort liability. These risks, however, can be readily mitigated via appropriate research and development. The serious legal impediment to commercializing bioprinted organs is the question of whether or not such organs are patentable.

The primary case law relevant to bioprinting's patentability is Diamond v Chakrabarty, a Supreme Court case from 1980 [66]. Under the two-prong test of Chakrabarty, a genetically engineered bacterium

capable of breaking down crude oil was found to be patentable because it was (A) non-naturally occurring and (B) the product of human ingenuity. Under this test, one could readily argue that a 3D printed organ constructed, layer-by-layer, from human stem cells may resemble a natural organ but contains more than ample structural differences to be considered non-natural. Also, as the assembly occurs exclusively due to the instructions of complex, human-written, computer code guiding the 3D printer, the process can also readily be argued to be the result of significant human ingenuity.

However, the elephant in the room for patentability is the America Invents Act (AIA) of 2011 [67]. This particular law has a section that states that no patent may issue on a claim directed to or encompassing a human organism. Because the AIA is more recent law, it expands upon the understanding established in Chakrabarty—meaning that the test today is now a three-prong test. To be patentable, a 3D bioprinted organ must be non-natural, the result of human ingenuity, and not a human organism. However, to date, neither the Act nor the Courts have defined "human organism" within the meaning of the AIA, so it remains up in the air whether the United States Patent Office (USPTO) will allow a patent on a bioprinted organ. Due to the statutes' ambiguous language, investors and researchers working with bioprinted organs should expect a legal challenge prior to patent issuance [68].

6. Conclusions and Recommendations

The opportunities offered for personalized medicine by 3D bioprinting and major technological advancements in tissue engineering including artificial skin [62] and cartilage [69] have been tissue engineered, and there have been advances in work on the printing of bone [70], parts of the ear [71], the urinary bladder [72], and heart valves [73]. However, all of these are relatively simple structures, and such techniques are not easily (if at all) transferrable to engineering complex solid organs, which are more applicable for drug testing applications and more in demand for organ replacement.

Another possibility exists if, instead of healthy tissue were to be bioprinted, one could add cancerous tissue and disease models [27] in order to study the efficacy of novel treatments outside the patient's body. By incorporating the patient's own cells, more accurate models and hence more effective treatments should result.

References

1. Advantages of Agile Work Strategies for Companies, Costs and Benefits. Available online: http://globalworkplaceanalytics.com/resources/costs-benefits (accessed on 5 March 2018).
2. Preliminary Statement of Policy Concerning Automated Vehicles. National Highway Traffic Safety Administration. Available online: https://www.nhtsa.gov/staticfiles/rulemaking/pdf/Automated_Vehicles_Policy.pdf (accessed on 26 February 2018).
3. Tomita, H. Awaiting the Realization of Fully Automated Vehicles: Potential Economic Effects and the Need for a New Economic and Social Design 2017. Available online: https://voxeu.org/article/potential-economic-and-social-effects-driverless-cars (accessed on 26 February 2018).

4. Godsmark, P. The Definitive Guide to the Levels of Automation in Driverless Cars 2017. Available online: https://driverless.wonderhowto.com/news/definitive-guide-levels-automation-for-driverless-cars-0176009/ (accessed on 2 March 2018).

5. Fleetwood, J. Public health, ethics, and autonomous vehicles. *Am. J. Public Health* **2017**, *107*, 532–537. [CrossRef] [PubMed]

6. Holstein, T.; Dodig-Crnkovic, G.; Pelliccione, P. Ethical and social aspects of self-driving cars. *arXiv* **2018**, arXiv:1802.04103.

7. World Economic Forum. This is How Much Time Americans Spend Commuting to Work. Available online: https://www.weforum.org/agenda/2016/03/this-is-how-much-time-americans-spend-commuting-to-work (accessed on 5 March 2018).

8. Clements, L.M.; Kockelman, K.M. Economic effects of automated vehicles. *Transp. Res. Rec. J. Transp. Res. Board* **2017**, *2606*, 106–114. [CrossRef]

9. Fagnant, D.J.; Kockelman, K. Preparing a nation for autonomous vehicles: Opportunities, barriers and policy recommendations for capitalizing on self-driven vehicles. *Transp. Res. Part A* **2015**, *77*, 167–181.

10. Mills, D.K. Future Medicine: The impact of 3D printing. *J. Nanomater. Mol. Nanotechnol.* **2015**, *4*, 1–3. [CrossRef]

11. Mills, D.K.; Tappa, K.; Jammalamadaka, M.; Weisman, J.A. Chapter 8: Medical Applications for 3D Printing. In *Advances in Manufacturing and Processing of Materials and Structures*; Taylor & Francis Group: Abingdon-on-Thames, UK, 2018.

12. Kang, H.-W.; Lee, S.J.; Ko, I.K.; Kengla, C.; Yoo, J.J.; Atala, A. A 3D bioprinting system to produce human-scale tissue constructs with structural integrity. *Nat. Biotechol.* **2016**, *34*, 312–319. [CrossRef] [PubMed]

13. Gross, B.C.; Erkal, J.L.; Lockwood, S.Y.; Chen, C.; Spence, D.M. Evaluation of 3D printing and Its potential impact on biotechnology and the chemical sciences. *Anal. Chem.* **2014**, *86*, 3240–3253. [CrossRef]

14. Facts and Myths. Available online: https://www.americantransplantfoundation.org/about-transplant/facts-and-myths/ (accessed on 9 March 2018).

15. Recommendation for Sustainable Kidney Care. Available online: http://ekha.eu/wp-content/uploads/2016/01/EKHA-Recs-for-Sustainable-Kidney-Care-25.08.2015.pdf (accessed on 8 September 2020).

16. Yanklowitz, S. Give a Kidney, Get a Check 2015. Available online: https://www.wsj.com/articles/give-a-kidney-get-a-kidney-1470265583/ (accessed on 23 March 2018).

17. USRDS. *2013 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*; National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Washington, DC, USA, 2014.

18. Shimazono, Y. The state of the international organ trade: A provisional picture based on integration of available information. *Bull. World Health Organ.* **2012**, *85*, 901–980. [CrossRef] [PubMed]

19. Small-Jordan, H. 2016 Organ Harvesting, Human Trafficking, and the Black Market. Available online: https://www.decodedscience.org/organ-harvesting-human-trafficking-black-market/56966 (accessed on 11 March 2018).

20. Leitner, T.; Capitani, L. *Investigations—Market for Black Market Organs Expands*; NBC Chicago: Chicago, IL, USA, 2016.

21. Munster, G. 2017 Here's When Having a Self-Driving Car Will Be a Normal Thing. Available online: http://fortune.com/2017/09/13/gm-cruise-self-driving-driverless-autonomous-cars/ (accessed on 9 March 2018).

22. Etherington, D. GM, Toyota Set to Push U.S. Regulators on Easing Self-Driving Restrictions 2017. Available online: https://techcrunch.com/2017/02/13/gm-toyota-set-to-push-u-s-regulators-on-easing-self-driving-restrictions/ (accessed on 13 February 2017).

23. Whitwam, R. Honda May Team up with Waymo to Make Self-Driving Cars 2016. Available online: https://www.extremetech.com/extreme/241556-honda-may-team-waymo-make-self-driving-cars (accessed on 23 December 2016).

24. Lynch, J.; Thibodeau, I. Filings: GM Plans 300 More Self-Driving Cars 2017. Available online: https://www.detroitnews.com/story/business/autos/general-motors/2017/04/14/gm-autonomous-fleet/100477110// (accessed on 14 April 2017).

25. O'Kane, S. Ford's New Autonomous Fusion Looks Freakishly Normal 2016. Available online: https://www.theverge.com/2016/12/28/14100278/ford-new-self-driving-car-fusion-hybrid-testing (accessed on 28 December 2016).

26. Davies, A. Uber's Self-Driving Truck Makes Its First Delivery: 50,000 Beers 2016. Available online: https://www.wired.com/2016/10/ubers-self-driving-truck-makes-first-delivery-50000-beers/ (accessed on 25 October 2016).
27. Lambert, F. Uber Self-Driving Prototype Rolls Over after Crash in Arizona, Police Says Uber is Not at Fault 2017. Available online: https://electrek.co/2017/03/25/uber-self-driving-prototype-accident-arizona/ (accessed on 25 February 2017).
28. Findling, D. CNBC Took BMW's New Self-Driving Car out for a Spin 2017. Available online: https://www.cnbc.com/2017/01/13/cnbc-took-bmws-new-self-driving-car-out-for-a-spin-heres-what-it-was-like.html (accessed on 14 January 2017).
29. Reuters. Forget Self-Driving Cars: Airbus will Test a Prototype for a Self-Flying Taxi by the End of This Year 2017. Available online: https://www.cnet.com/news/forget-self-driving-cars-how-about-a-self-flying-taxi/ (accessed on 16 January 2017).
30. Lambert, F. Tesla Hints at Testing Self-Driving Car Prototypes outside of California 2017. Available online: https://electrek.co/2017/02/06/tesla-testing-self-driving-car-prototypes-outside-california// (accessed on 6 February 2017).
31. Burgess, M. We Went Off-Road in Jaguar Land Rover's Autonomous Car 2016. Available online: https://www.wired.co.uk/article/self-driving-autonomous-land-rover-jaguar-technology (accessed on 22 July 2016).
32. McMahon, T. Long Term U.S. Inflation 2014. Available online: https://inflationdata.com/inflation/inflation_rate/long_term_inflation.asp (accessed on 1 April 2014).
33. WHO (World Health Organization). GKT1 Activities and Practices. Available online: http://www.who.int/transplantation/gkt/statistics/en/ (accessed on 14 April 2018).
34. Global Observatory on Donation and Transplantation. Available online: http://www.transplant-observatory.org (accessed on 14 April 2018).
35. U.S. Renal Data System, USRDS.UC San Francisco Dept. of Bioengineering & Therapeutic Sciences. The Kidney Project. In *2013 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*; National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Washington, DC, USA, 2014; Available online: https://pharm.ucsf.edu/kidney/need/statistics (accessed on 4 April 2017).
36. National Kidney Foundation Organ Donation and Transplantation Statistics. Available online: https://www.kidney.org/news/newsroom/factsheets/Organ-Donation-and-Transplantation-Stats (accessed on 14 April 2018).
37. Ren, X.; Ott, H.C. Pflugers on the road to bioartificial organs. *Arch. Eur. J. Physiol.* **2014**, *466*, 1847. [CrossRef]
38. Atala, A.; Kasper, F.K.; Mikos, A.G. Engineering complex tissues. *Sci. Transl. Med.* **2012**, *4*, 160rv112. [CrossRef]
39. Iwamuro, M.; Shiraha, H.; Nakaji, S.; Yamamoto, K. Prospects for creating bioartificial liver system with induced pluripotent stem cell technology. *Biotechnol. Biomater.* **2013**, *3*, 157. [CrossRef]
40. Carpentier, B.; Gautier, A.; Legallais, C. Artificial and bioartificial liver devices: Present and future. *Gut* **2009**, *58*, 1690–1702. [CrossRef] [PubMed]
41. Reddy, M.; Herrero, P.; El Sharkawy, M.; Pesl, P.; Jugnee, N.; Thomson, H.; Pavitt, D.; Toumazou, C.; Johnston, D.; Georgiou, P.; et al. Feasibility study of a bio-inspired artificial pancreas in adults with Type 1 diabetes. *Diabetes Tech. Ther.* **2014**, *16*, 550–557. [CrossRef] [PubMed]
42. The Kideny Project. Available online: https://pharm.ucsf.edu/kidney (accessed on 14 March 2018).
43. Weymann, A.; Patil, N.P.; Sabashnikov, A.; Jungebluth, P.; Korkmaz, S.; Li, S.; Veres, G.; Soós, P.; Ishtok, R.; Chaimow, N.; et al. Bioartificial heart: A human-sized porcine model—The way ahead. *PLoS ONE* **2014**, *9*, e111591. [CrossRef]
44. Jessop, Z.M.; Al-Sabah, A.; Gardiner, M.D.; Combellack, E.; Hawkins, K.; Whitaker, I.S. 3D bioprinting for reconstructive surgery: Principles, applications and challenges. *J. Plast. Reconstr. Aesthetic Surg.* **2017**, *70*, 1155–1170. [CrossRef] [PubMed]
45. Murphy, S.V.; Atala, A. 3D bioprinting of tissues and organs. *Nat. Biotechnol.* **2014**, *32*, 773–785. [CrossRef]
46. Ringeisen, B.R.; Othon, C.M.; Barron, J.A.; Wu, P.K.; Spargo, B.J. The evolution of cell printing. In *Fundamentals of Tissue Engineering and Regenerative Medicine*; Meyer, U., Handschel, J., Wiesmann, P.H., Eds.; Springer: Berlin/Heidelberg, Germany, 2009; pp. 613–631.
47. Guillemot, F.; Mironov, V.; Nakamura, M. Bioprinting is coming of age: Report from the International Conference on Bioprinting and Biofabrication in Bordeaux (3B'09). *Biofabrication* **2010**, *2*, 1–7. [CrossRef]

48. Groll, J.; Boland, T.; Blunk, T.; Burdick, J.A.; Cho, D.W.; Dalton, P.D.; Derby, B.; Forgacs, G.; Li, Q.; Mironov, V.A. Biofabrication: Reappraising the definition of an evolving field. *Biofabrication* **2016**, *8*, 13001. [CrossRef]

49. Bajaj, P.; Schweller, R.M.; Khademhosseini, A.; West, J.L.; Bashir, R. 3D biofabrication strategies for tissue engineering and regenerative medicine. *Annu. Rev. Biomed. Eng.* **2014**, *16*, 247–276. [CrossRef]

50. Derakhshanfar, S.; Mbeleck, R.; Xu, K.; Zhang, X.; Zhong, W.; Xing, M. 3D bioprinting for biomedical devices and tissue engineering: A review of recent trends and advances. *Bioact. Mater.* **2018**, *3*, 144–156. [CrossRef]

51. Bioprinting is Coming of Age. Available online: https://www.shapingtomorrow.com/home/alert/225863-Bioprinting-is-coming-of-age (accessed on 8 September 2020).

52. Bishop, E.S.; Mostafa, S.; Pakvasa, M.; Luu, H.H.; Lee, M.J.; Wolf, J.M.; Ameer, G.A.; He, T.-C.; Reid, R.R. 3-D bioprinting technologies in tissue engineering and regenerative medicine: Current and future trends. *Genes Disease* **2017**, *4*, 185–195. [CrossRef] [PubMed]

53. Yang, E.; Miao, S.; Zhong, J.; Zhang, Z.; Mills, D.K.; Zhang, L.G. Bio-based polymers for 3D printing of bioscaffolds. *Poly Rev.* **2018**, *58*, 668–687. [CrossRef] [PubMed]

54. Faramarzi, N.; Yazdi, I.K.; Nabavinia, M.; Gemma, A.; Fanelli, A.; Caizzone, A.; Ptaszek, L.M.; Sinha, I.; Khademhosseini, A.; Ruskin, J.N.; et al. Patient—Specific bioinks for 3D bioprinting of tissue engineering scaffolds. *Adv. Healthc. Mater.* **2018**, *7*, 1701347. [CrossRef] [PubMed]

55. Chimene, D.; Lennox, K.K.; Kaunas, R.; Gaharwar, A.K. Advanced bioinks for 3D printing: A materials science perspective. *Ann. Biomed. Eng.* **2016**, *44*, 2090–2102. [CrossRef]

56. Mironov, V.; Trusk, T.; Kasyanov, V.; Little, S.; Swaja, R.; Markwald, R. Biofabrication: A 21st century manufacturing paradigm. *Biofabrication* **2009**, *1*, 22001. [CrossRef]

57. Shim, J.-H.; Lee, J.-S.; Kim, J.Y.; Cho, D.-W. (2012) Bioprinting of a mechanically enhanced three-dimensional dual cell-laden construct for osteochondral tissue engineering using a multihead tissue/organ building system. *J. Micromech. Microeng.* **2012**, *22*, 85014. [CrossRef]

58. Mobaraki, M.; Maryam, M.; Yazdanpanah, A.; Luo, Y.; Mills, D.K. Bioinks and bioprinting: A focused review. *Bioprinting* **2020**, *18*, e00080. [CrossRef]

59. Gopinathan, J.; Noh, I. Recent trends in bioinks for 3D printing. *Biomater. Res.* **2018**, *22*, 11. [CrossRef]

60. Gungor-Ozkerim, P.S.; Inci, I.; Zhang, Y.S.; Khademhosseini, A.; Dokmeci, M.R. Bioinks for 3D bioprinting: An overview. *Biomater. Sci.* **2018**, *6*, 915–946. [CrossRef]

61. Shim, J.-H.; Kim, J.Y.; Park, M.; Park, J.; Cho, D.-W. Development of a hybrid scaffold with synthetic biomaterials and hydrogel using solid freeform fabrication technology. *Biofabrication* **2011**, *3*, 34102. [CrossRef]

62. Cheng, R.Y.; Eylert, G.; Gariepy, J.M.; He, S.; Ahmad, H.; Gao, Y.; Priore, S.; Hakimi, N.; Jeschke, M.; Günther, A. Handheld instrument for wound-conformal delivery of skin precursor sheets improves healing in full-thickness burns. *Biofabrication* **2020**, *12*, 25002. [CrossRef]

63. Feildena, E.; Tuñón Blancaa, E.-G.; Giuliania, F.; Saiza, E.; Vandeperrea, L. Robocasting of structural ceramic parts with hydrogel inks. *J. Eur. Ceram. Soc. March* **2016**, *32*, 2525–2533. [CrossRef]

64. Peng, W.; Datta, P.; Ayan, B.; Ozbolat, V.; Sosnoski, D.; Ozbolat, I.T. 3D bioprinting for drug discovery and development in pharmaceutics. *Acta Biomater.* **2017**, *57*, 26–46. [CrossRef] [PubMed]

65. Ma, X.; Liu, J.; Zhu, W.; Tang, M.; Lawrence, N.; Yu, C.; Gou, M.; Chen, S. 3D bioprinting of functional tissue models for personalized drug screening and in vitro disease modeling. *Adv. Drug Deliv. Rev.* **2018**, *132*, 235–251. [CrossRef] [PubMed]

66. Daimond vs. Charbartgy. Available online: https://www.oyez.org/cases/1979/79-136 (accessed on 20 May 2020).

67. H.R.1249—Leahy-Smith America Invents Act. Available online: https://www.congress.gov/bill/112th-congress/house-bill/1249 (accessed on 9 June 2020).

68. Kelly, E. FDA regulations of 3D printed organs and associated ethical challenges. *Univ. Pa. Law Rev.* **2018**, *166*, 516–545.

69. Galarraga, J.H.; Kwon, M.Y.; Burdick, J.A. 3D bioprinting via an in situ crosslinking technique towards engineering cartilage tissue. *Sci. Rep.* **2019**, *9*, 19987. [CrossRef]

70. Tang, D.; Tare, R.; Yang, L.-Y.; Williams, D.F.; Ou, K.-L.; Oreffo, R.O. Biofabrication of bone tissue: Approaches, challenges and translation for bone regeneration. *Biomaterials* **2018**, *83*, 363–382. [CrossRef] [PubMed]

71. Mussi, E.; Furferi, R.; Volpe, Y.; Facchini, F.; McGreevy, K.S.; Uccheddu, F. Ear reconstruction simulation: From handcrafting to 3D printing. *Bioengineering* **2019**, *6*, 14. [CrossRef]

72. Jana, S.; Lerman, A. Bioprinting a cardiac valve. *Biotechnol. Adv.* **2015**, *33*, 1503–1521. [CrossRef]
73. Atala, A.; Bauer, S.B.; Soker, S.; Yoo, J.J.; Retik, A.B. Tissue-engineered autologous bladders for patients needing cystoplasty. *Lancet* **2006**, *367*, 1241–1246. [CrossRef]