Three-Dimensional Printing in Plastic and Reconstructive Surgery

A Systematic Review

Adam J. Bauermeister, MD, Alexander Zuriarrain, MD, and Martin I. Newman, MD, FACS

Background: Increasingly affordable three-dimensional (3D) printing technologies now make it possible for surgeons to create highly customizable patient-tailored products. This process provides the potential to produce individualized artificial and biologic implants, regenerative scaffolds, and cell-specific replacement tissue and organs. The combination of accurate volumetric analysis and production of 3D printed biologic materials are evolving techniques that demonstrate great promise in achieving an accurate and naturally appearing anthropomorphic reconstruction. This systematic review summarizes the current published literature and known ongoing research on 3D printing in the field of plastic and reconstructive surgery (PRS).

Methods: Three medical databases (PubMed, Ovid MEDLINE, and Google Scholar) as well as recent news articles and university websites were searched using PRS and industry-related search terms. Inclusion criteria consisted of any publication or reputable news or academic article in electronic or printed media directly studying or commenting on the use of 3D printing technology in relation to PRS. The current literature was critically appraised, and quality of selected articles was assessed and manually filtered for relevance by 2 reviewers.

Results: A total of 1092 articles were identified from the aforementioned sources discussing 3D printing in medicine. The 3D printing in relation to biologic and surgical applications was discussed in 226 articles. Within this subset, 103 articles were included in the review. Of those selected, 5 were pertinent to surgical planning, training, and patient education; 4 to upper extremity and hand prosthetics; 24 to bone and craniomaxillofacial (CMF) reconstruction; 10 to breast reconstruction; 20 to nose, ear, and cartilage reconstruction; 20 to skin; and finally 20 involving overlapping general topics in 3D printing and PRS.

Conclusions: The 3D printing provides the ability to construct complex individualized implants that not only improve patient outcomes but also increase economic feasibility. The technology offers a potential level of accessibility that is paramount for remote and resource-limited locations where health care is most often limited. The 3D printing-based technologies will have an immense impact on the reconstruction of traumatic injuries, facial and limb prosthetic development, as well as advancements in biologic and synthetic implants.

Key Words: 3D printing, 3D bioprinting, additive manufacturing, implant development, plastic and reconstructive surgery

(*Ann Plast Surg* 2015;00: 00–00)

In the last decade, three-dimensional (3D) printing has rapidly grown to become a leading power in the industrial manufacturing field. This flourishing industry netted multiple billions during 2012 and has been forecasted to exceed US $10.8 billion in 2021.[1] Since its invention in the 1980s, this technology has become an integral tool in the rapid prototyping and manufacturing of items ranging from clothes and furniture to the construction of houses, cars, aircraft, and weaponry.[2–6] Considering its substantial financial base, related research funding over the years has resulted in radical improvements in this technology. With these improvements, novel applications have been created for its use in the fields of biology and medicine. Significant strides have already been seen in the areas of tissue engineering and implant development, both of which demonstrate great potential for the field of plastic and reconstructive surgery (PRS).

Three-dimensional printing is a form of additive or subtractive manufacturing, which is a precise computer-controlled process where either successive layering of material is deposited or carved away to produce a 3D end product. A multitude of materials ranging from titanium alloys to collagen can be used with this method. The addition of increasingly affordable 3D scanning technology and software makes it possible for physicians and surgeons to create highly customizable patient-tailored products. Currently, this tool is being used more routinely in surgical planning, patient education, and custom prosthetic development. However, this process provides the potential to produce everything from artificial and biologic implants, regenerative scaffolds for wound healing, to cell-specific replacement tissue and organs.

METHODS

A systematic review of the literature was conducted to evaluate all current published reports and ongoing research regarding 3D printing technology (additive/subtractive manufacturing) in relation to PRS. Inclusion criteria consisted of any publication or reputable news or academic article in electronic or printed media directly studying or commenting on the use of 3D printing or bioprinting technology in relation to its use in associated fields or application in PRS. Three medical databases (PubMed, Ovid MEDLINE, and Google Scholar) as well as recent news articles and university websites were searched using PRS and industry-related search terms. The current literature was critically appraised, and the quality of select articles was assessed and manually filtered for relevance by 2 reviewers. Only studies printed in English were included.

RESULTS

A total of 1092 articles were identified from the aforementioned sources discussing 3D printing in medicine. Two hundred twenty-six discussed 3D printing in relation to biologic and surgical applications. Within this subset, 103 articles were included in the review. Articles selected were related to fields of PRS, involved and/or discussed potential clinical applications, and were considered to be of reputable source. Articles chosen dated from 2005 to 2015. Of those selected, 5 were pertinent to surgical planning, training, and patient education; 4 were related to upper extremity and hand prosthetics; 24 to bone and CMF reconstruction; 10 to breast reconstruction; 20 to nose, ear, and cartilage reconstruction; 20 to skin; and finally 20 involving overlapping general topics in 3D printing and PRS. Twenty-one additional articles that were notable but not directly related to PRS were included as ancillary supportive literature.

DISCUSSION

Applications

Three-dimensional printing has recently become popular in the media and scientific literature. Reports have highlighted the manufacture of cutting-edge, highly customized devices, such as tracheobronchial splints, bionic ears, and more recently, the increasing feasibility

Received June 16, 2015, and accepted for publication, after revision October 12, 2015.
From the Department of Plastic and Reconstructive Surgery, Cleveland Clinic Florida, Weston, FL.
Conflicts of interest and sources of funding: none declared.
Reprints: Adam J. Bauermeister, MD, Cleveland Clinic Florida 2950 Cleveland Clinic Blvd Weston, FL 33331. E-mail: adambauermeister@gmail.com.

ISSN: 0148-7043/15/0000–0000
DOI: 10.1097/SAP.0000000000000671

of 3D printed soft tissues and organs.[7–9] Outside of these advanced applications, 3D printing offers the prospective of producing inexpensive and more accessible devices for the medical community. Recent publications have described 3D printing clinical applications in a range of objects, such as arm prostheses, bone implants, and anatomical reconstructions, to facilitate in surgical education, clinical planning, and patient education.[10]

Surgical Planning and Training

Planning Difficult Surgeries

Because of the unique clinical situations that face plastic and reconstructive surgeons, the use of 3D printing has sparked a tremendous amount of hope for the treatment of very complex disease processes. An example of one such potentially lethal disorder is known as cloverleaf skull deformity. There are now reports of reconstructive surgeons in Brazil using 3D printing technology to enhance their preoperative planning for a more successful perioperative and postoperative course.[11]

The online article discusses the story of Dr. Jorge Vicente Lopes da Silva who leads the Tridimensional Technologies Division at the Center for Information Technology Renato Archer in Sao Paulo, Brazil. Using 3D printing technology, the craniofacial plastic surgery and pediatric neurosurgery units of the Beneficencia Portuguesa Hospital were able to benefit from a successfully created 3D reconstruction of a child's skull with a cloverleaf deformity. The technology enabled the surgical teams to approach a very complex structural problem and formulate a tailored treatment plan with added confidence.

The 3D modeling is an efficient means of demonstrating spatial relationships to surrounding structures. The ability to visualize critical structures before a complex operation allows the surgeon to decrease the rate of complications.[12]

Resident Training

Rapid prototyping is an evolving technology that has the potential to revolutionize medical education. As plastic surgeons, we are expected to understand the nuances of detailed human anatomical structures and their spatial relationship with one another. The 3D printing can allow for an in-depth understanding of human anatomy that was traditionally gleaned from textbook drawings and years of surgical experience performing complex dissections. The future of plastic surgery education is exciting because of the ability to take a 2-dimensional (2D) image and bring it to life with a full-scale model.[12]

In a study published in the *Journal of Surgical Education* in 2014, Dr. Watson and his team from the University of North Carolina at Chapel Hill discuss the use of 3D printing to create personalized, patient-specific, hepatic models for surgical resident education. They were able to create multiple patient-specific preoperative 3D physical models of portal and hepatic venous anatomy at a cost of less than US $100 per model. In their discussion, they emphasize the ability to not only examine the models visually but also to gain details from our sense of touch. These models allow our visual and tactile senses to unite, providing a more extensive understanding. The eventual goal would be to create inexpensive disposable models that would allow surgeons-in-training to dissect the models and discard them once the techniques have been mastered.[13]

PATIENT EDUCATION

A very important aspect of the successful practice of PRS is the ability to manage patient expectations. In order to help patients understand their disease process and what can be done surgically to treat them, we currently rely on 2D images on a flat screen. Many times, patients do not understand the true nature of their medical condition, which leads to frustration and poor outcomes.

The 3D modeling has the capacity to create exact models of a patient's anatomic deformity and serve as an indispensable tool when educating patients. When patients can use their sense of touch to hold a printed model and compare it with a model of their postoperative outcome, they can more realistically manage their expectations.[12]

ARM AND HAND PROSTHETICS

Nearly 2 million people in the United States have lost at least 1 limb according to the Amputee Coalition.[14] About 185,000 amputations are conducted in the United States each year.[15] There is a serious need for more affordable and available extremity prosthetics in this country. The ability to create customized devices has led to the rapid development of additive manufacturing. One can imagine that the ability to design and build devices that can then be used for surgical reconstruction would be a significant advance in modern medicine. One of the areas that would be impacted most significantly would be wounded war veterans who have suffered the loss of a limb. Perhaps in the future, this technology could be used to fabricate a prosthetic arm and/or hand that would be specifically tailored to an individual patient's anatomical need.

The use of implants in hand surgery would also be affected by the use of 3D printing. Currently, interphalangeal joint implants are made in a finite number of sizes that do not always provide a perfect match for every patient. Customized joint implants with this technology for all types of joints would be highly beneficial. The complex anatomy of the hand and its component parts demand close attention to detail that could be provided by rapid prototyping.

A South African company by the name of Robohand is producing printable hands and fingers. They state that they have enabled over 200 individuals with their 3D printed prosthetics. The company combines thermoplastic, aluminum, and stainless steel digits to create a mechanical and fully functional hand(s)/ finger(s). Robohand has also collaborated with US entrepreneur Mike Ebeling to produce affordable printed arms for war amputees in Sudan. These printed extremities are said to have a minimal cost of US $100.[16,17]

The World Health Organization states that there are one billion people with disabilities in the world.[18] Along these lines, Google has promised US $20 million in grants to nonprofits using emerging technologies to help the disabled.[19] The Google Impact Challenge: Disabilities program launched in May of 2015 has given a US $600,000 grant to Enable, an organization that uses volunteers to design, print, assemble, and fit 3D-printed upper-limb prosthetics at no cost. Google.org Director Jacqueline Fuller recently wrote in a Google blog that the Impact Challenge "will seek out nonprofits and help them find new solutions to some serious 'what ifs' for the disabled community".

BONE AND CMF

There has been a substantial need for personalized medicine to produce a genuinely individualized, yet economic, solution to facial reconstruction. The CMF bone defects create a unique challenge that can be attributed to the highly complex geometry of this subset of bones.[20,21] Current preferred treatments use autologous bone grafts which require bone harvesting from another location and limits the ability to aesthetically reproduce unique facial features. Bone harvesting is restricted by size and may result in complications, such as pain, infection, or functional disability.[22]

The distinct anatomy of the face provides an ideal case where an exceedingly individualized implant would be essential. The 3D printed implant provides a new level of anatomical precision and delivers an entirely individualized solution for facial reconstruction. Facial injuries that previously required multiple surgeries, imprecisely fitting plating systems, or bone grafts to repair can now be accurately fitted with a single-component implant that can substantially increase the structural integrity and cosmesis of the reconstruction.

Synthetic Implants

One of the first clinical applications of 3D printed medical implants has been in the field of CMF reconstruction and orthopedics. The 3D printed vertebrae, hips, pelvis, and mandibular implants have now been performed.[23–27] One medical company, Medical 4WEB, has recently reported the implantation of over 3000 of their 3D printed orthopedic trusses.[28] A recent example of the use of this technology in CMF reconstruction was with the successful implantation of a complete 3D printed cranial vault in a 22-year-old female patient with van Buchem disease, a rare condition that causes severe cranial bone thickening.[29] The patient who had already lost her vision from the disease and would have ultimately died from it received a custom implant that allowed her to regain her vision and return to work within months of her operation.

Multiple other CMF reconstruction procedures have been performed successfully over the last several years under experimental premises with the use of 3D printed plastic and titanium implants. Tissue-engineered bone grafts are an advancement in this technology that may permit more mainstream utilization. They provide a promising alternative that allows for accurate tailoring of the graft's shape which eliminates the need for additional surgeries and resultant comorbidities.[30–36] Synthetic and biologic scaffolds have been used for bone regeneration, each with their relative advantages and disadvantages.

Synthetically produced scaffolds may not precisely mimic the biochemical or structural properties of the native scaffold but allow for greater control in their fabrication process and more reliable reproducibility.[37] The material properties, bioactivity, porosity, and shape of synthetic grafts can be closely controlled and customized for specific applications. Several new materials have emerged as favorable polymers for scaffold fabrications, such as polycaprolactone (PCL) and polyetherketoneketone. The PCL has shown to be biocompatible and safely degrades in the body at a similar rate to new bone formation and has already received regulatory approval for certain applications.[38,39] Oxford Performance Materials is one of the first to receive Food and Drug Administration approval for use of 3D printed cranial facial implants in the United States.[40] The implants are constructed from a polyetherketoneketone polymer which is both biocompatible and osteoconductive, promoting osteocyte attachment, activity, and implant incorporation.

Biologic Implants

Biologic scaffolds alternatively provide improved osteoconductive properties and better implant incorporation with the potential of increase longevity. Previously, the treatment of these defects were clinically challenging due to the limited availability of transplantable autologous bone grafts and the complexity of facial bone geometry. Advances in bone tissue engineering now provide alternatives using biocompatible scaffold materials and autologous cells.

This approach uses CT imaging to create 3D renderings of the patient's skeletal structure that is then used as a map to guide either a 3D subtractive or additive fabrication device. In the subtractive method, the device shapes media created from decellularized bovine bone that is stripped free of its native cells to produce a bare calcium hydroxylapatite scaffold. This technology, based off 15 years of National Institute of Health-funded research on bone tissue engineering, is being used at Columbia University and at an NYC based Biotech Company called EpiBone.[37,41,42]

The additive method produces a 3D model from sequential layering of mineralized or bioabsorbable material. This alternate avenue bypasses the need of a bone decellularization process and circumvents size restrictions generated by the substrate material seen in the subtractive process. Once the scaffold is shaped to form an identical model of the original bone, it is then impregnated with stem cells isolated from the patient's bone marrow or fat tissue. The new bone is either incubated in vivo in the patient or placed into a bioreactor for maturation. The bioreactor provides sufficient oxygenation and nutrients to allow for the production of a viable bone that is then later ready for implantation into the patient.

Successful in vivo graft incorporation using this approach has been seen with consecutive animal trials at Washington State University and Wake Forest University.[43–47] Implants were seen to mature in vivo and form mineralized tissues with similar density and structure to that of endogenous bone tissue. Approval for human implantation of 3D printed bioartificial scaffolds have now been attained by a Swiss company called RegenHU.[48,49] Research currently underway with large animals will establish safety and feasibility before further commercialization in the coming years.

Multiple reports have demonstrated that several different printable substrates have supported the induction of human adipose derived stem cells to form vasculature and functional bone tissue.[41,50–52] This has been an essential step in demonstrating the capabilities and potential of these grafts while bypassing the resulting comorbidities and size restrictions of traditional bone graft harvesting. This technology promises precise anatomical patient specific implants that can continue to remodel and integrate into the body providing the prospect for greater durability and a more accurate reconstruction.

BREAST

3D Imaging and Volume Assessment

Analysis of 3D imaging provides personalized consideration of variations in anatomy, such as muscular and skeletal asymmetries, that may cause unexpected aesthetic outcomes upon breast implantation. The current standard for preoperative evaluation in selecting appropriate implant volume and shape as well as determining breast flap location involves the use of 2D photography and visual estimation. More objective methods, such as direct anthropomorphic measurements or 3D photography, have been tried in the past with variable results.[53] Researchers are now using CT or MRI imaging for more accurate volumetric analysis and to produce inexpensive 3D printed haptic models for tactile feedback and operative guidance.[54,55] These studies demonstrated that 3D imaging provided a useful tool for more accurate volume measurements, shape analysis, and for evaluation of symmetry. The technique assists in determining THE causes of asymmetry and helps guide reconstruction prior to surgery. When compared with other methods of volume assessment, 3D modeling and MRI showed to be the most accurate and reliable tools in evaluating breast volume.[56] Concurrent contrast use provides preoperative identification of vascular anatomical variations and assesses perforator locations for deep inferior epigastric perforators and transverse rectus abdominis myocutaneous flap reconstruction.[57] In addition to aiding in preoperative planning, data from imaging can then be used in the digital reconstructions necessary for 3D printed implant fabrication.

Synthetic Implants

A range of standardized breast implants with different profiles, shapes, and sizes are commercially available; however, they may not be well suited for all patients. Multiple studies have confirmed that most women have some degree of breast asymmetry with some large series reporting noticeable breast asymmetry in up to 81% to 88% of their patient population.[58,59] These asymmetries can be primarily due to respective discrepancies in the overall size or shape of the breast or nipple areolar complex.[60] Breast asymmetries may also arise secondarily to underlying bone or soft tissue abnormalities of the thoracic chest wall.

Considering the overall prevalence of breast asymmetry, literature has also demonstrated significant corresponding postoperative discrepancies in breast size and shape after mammaplasty procedures.[61] Authors note that preexisting asymmetries often times will produce more pronounced differences postoperatively even with the use of initial corrective measures. Another study reveals that 27% of patients who seek revisionary breast surgery do so because of concerns of breast asymmetry.[62] A large Danish study of 5373 women with primary cosmetic breast augmentation also remark that asymmetry was one of the most frequent reasons for reoperation with exchange or removal of implant.[63]

These findings underscore the importance and emphasize the need for a customized breast implant that can more accurately compliment anatomical variations to produce more uniform aesthetic outcomes for individuals who do not fit within the standard range of implant sizes or who have noticeable breast asymmetries. Postmastectomy or lumpectomy patients seeking reconstructive surgeries have even more discernible differences that may prove to be an added challenge in creating a consistently balanced appearance. Often times, the underlying cause of the asymmetry is difficult to assess clinically. Preoperative imaging, as discussed above, is beneficial in these situations providing a conclusive method of determining the proportion of asymmetry that is due to differences in soft tissue volume or chest wall shape. This method helps produce exact implants that are tailored to fit the particular needs of that patient.[64]

In addition to providing precisely shaped implants for patients, 3D printing also allows physicians the ability to produce implants with stratified density layering. Additive printing has the capability of using variable density substrates that can then be layered in a particular order with the added option of using different surface textures to create a totally integrated single-component implant. This allows for a more proportional correction of asymmetries with particular densities assigned to match the fraction of analogous soft tissue and/or chest wall differences. Stratified density layering also provides the ability to create a firmer posterior base and interior quadrant to match the inner ligamentous lobular portions of the breast to produce more lift and projection while allowing for a less dense exterior to preserve an overall natural feeling of the implant. This technology provides the potential to create superior aesthetic outcomes and more natural tactile implant qualities as a result of individual tailoring to accommodate the patient's anatomical needs.

Biologic Implants

Doctors in the Biomedical Engineering Department at University of Texas are working with TeVido BioDevices toward developing 3D bioprinted breast implants.[65] Current development is focused on already-patented biomatrices to be used for nipple areola complex reconstruction and in custom volumetric replacement of lumpectomy defects.[66,67] These areas have proven to be problematic in the past with unpredictable breast volumes from variable fat graft resorption and potential foreign body responses with use of artificial implants. The nipple areolar complex has also been another point of contention with often time's unsatisfactory aesthetic results from nipple tattooing alone, and methods to reconstruct nipple projection have proven unreliable in a number of cases with risk of implant extrusion or skin erosion from use of silicon nipple implants. The use of a biological implant that can be incorporated into the body avoids these potential complications and provides a much-needed solution to this common issue that many women face.

The premise behind the technology is the use of an absorbable biologic matrix that is then impregnated with autografted lipocytes from the patient's abdomen. The implant, which is specifically designed to fill the defect, allows for correct regional volume proportions and permits implant incorporation into the surrounding tissues. Microtubular structures throughout the implant provide influx of blood and bionutrients to potentially increase lipocyte viability compared with that of fat grafting alone. Although this development is currently undergoing animal trials, it has recently received major National Institute of Health funding to reach its eventual goal of entering clinical trials in the next coming years. The future aim is to develop biologic breast implants with natural feel, customized proportions and projection, as well as utilization of denser biologic substrates such as collagen to provide sustained firmness and resilience against future ptosis.

Researchers at Queensland University of Technology in Brisbane, Australia, are concurrently working on bioabsorbable 3D printed scaffolds for breast reconstruction.[68] Their approach is similar to that of the one taken by TeVido BioDevices. Professors at the university state that use their technology for entire breast reconstruction in former cancer patients could be ready in the next coming years. The 3D printed scaffolds are based on the MRI reconstruction of the contralateral breast and designed to dissolve over a 2- to 3-year span as fatty breast tissue regenerates.

NOSE AND EARS

Prosthetics

The first known use of facial prosthetics dates back to Egypt in 500 B.C. with the use of wax and earthen ceramics in creating prosthetic eyes, ears, and noses.[69] Today, specialists, known as clinical anaplastologists, make realistic prostheses to modify disfigured or missing anatomy and to allow patients to maintain social interactions while decreasing personal discomfort. Conventional facial prostheses require artistic and technically skilled individuals to create and may take weeks to produce. Costs can range from US $10,000 to US $15,000 per device, frequently not reimbursed by health insurance, and are often times imperfect and visually distinguishable from the original anatomical counterpart.[70]

The 3D printing has drastically changed the field of facial prosthetics by allowing the manufacturing of extremely detailed life-like replicas of facial features that can be produced within hours and are a small fraction of the cost of traditional prosthetics. The 3D printing costs can be minimal, with the first item being as inexpensive as the last.[71] This is especially true for small-sized custom implants or prosthetics, such as those used for craniofacial disorders.[72] One study showed that using particular 3D printing methods with high-quality silicone soft prostheses with complicated structures could be fabricated with a desktop 3D printer at a very low cost. Using this method, the total cost of manufacturing an ear prosthesis is approximately US $30.[73]

The technology is already available and currently being used by a number of institutes, some of which include the University of Miami, Fripp Design and Research (UK), and University of Sheffield (UK).[74,75] The process is accomplished with the use of inexpensive mobile topographic scanners or stereophotogrammetry to map the undamaged side of the patient's face. The software then creates mirror images of the scanned surface and translates it to a 3D printer to produce the implant. Silicone rubber devices are printed infused with colored pigments matching the patient's skin tone. Composite materials reinforced with nanoparticles provide improved durability and closer skin color matching when compared with conventional prosthesis. Mobile scanning devices allow for worldwide availability and easy replacement. Once data are downloaded, the prosthetic can be printed and shipped to the patient by the next day.[75]

Biologic Implants

There are very few satisfactory solutions for facial soft tissue reconstruction. Major nose and ear deformities caused by trauma, cancer, or congenital abnormalities are usually reconstructed using synthetic implants of unnatural consistency which may produce foreign body reactions leading to infection or erosion of the implant from the skin. The specific anatomy of the nose and ears is especially prone to these complications due to their limited blood supply and overlying thinness of skin. Other approaches that involve cartilage harvested from ribs often times is painful for the patient and technically difficult to perform with the reconstruction rarely appearing completely natural or performing well resulting in potential donor site defects, morbidity, and scars. Bioengineers and physicians at Cornell University, Columbia University, Wake Forest Institute for Regenerative Medicine, and University College of London (UCL) are working toward finding a solution to this problem by producing 3D printed biocompatible implants. These developments have a great potential for the medical field not only for weight-bearing cartilage implants but also soft tissue reconstructive and cosmetic procedures, such as otoplasties and rhinoplasties.

Cornell University is using 3D printed injectable gels made of living cells to produce flexible ears that grow cartilage.[76] Over a 3-month period, these constructs grew cartilage to replace the collagen used to mold them. The 3D imaging of a patient's ear was used to assemble a high-density gel mold by way of additive printing. The mold was injected with murine-derived collagen and bovine cartilage cells which over a 3-month period quickly grew to form a living cartilaginous copy of the original imaged ear. Researchers are broadening their work toward constructing other cartilaginous structures, such as joints, trachea, spine, and nose, with more recent research expanding to the successful use of human chondrocytes.[77] Safety and efficacy tests that are currently underway must first be completed before the first human trials can be possible.

Wake Forest Institute for Regenerative Medicine are working to cover 3D printed porous bioscaffolds developed in the laboratory with a patient's own cartilage cells before implantation. This approach is very similar to that of Cornell University; however, they are combining a new hybrid technology that should provide a level of durability of the collagen construct that is comparable to native cartilage.[78] The research team's discovery mixes electrospinning, a method of creating polymer-based nanoscale fibrous materials with bioprinters. Alternate layering of the electrospun material with the printed biogels provides additional structure and strength needed to support the loads that cartilage carries while still allowing flexibility and promoting cellular growth. The 3D printed constructs were implanted into the mice and was studied over a period of several months. The implants demonstrated equivocal mechanical strength and developed similar cellular structures when compared with that of natural cartilage. Additional studies carried out by other institutes have also demonstrated similar increased durability of 3D printed cartilage constructs when using the microspinning/hydrogel hybrid models.[79]

Columbia University has created 3D printed scaffolds that induce fibrochondrocytic differentiation of endogenous cells for knee meniscus regeneration.[80] The MRI scans of intact undamaged meniscus were used to produce anatomically correct 3D printed scaffolds. The process allowed for sequential layering and regional distribution of mesenchymal progenitor cells, tissue growth factors, and supportive substrates. Subsequent fibrochondrocyte differentiation followed with concurrent synthesis of spatially incorporated zone-specific collagen types. These cellularly infused implants were inserted into the knees of sheep replacing their native meniscus. After 3 months, the treated animals were walking normally. Postmortem analysis demonstrated completely regenerated meniscus with structural and mechanical properties very similar to that of the natural meniscus. The therapy could provide the first effective and long-lasting solution to joint injuries and confer better understanding in the development of a reliable collagen implant technology.

The UCL is using similar technology to produce biocompatible 3D printed ears.[81] Unlike the above-discussed implants, UCL is using hybrid implants constructed from a lightweight synthetic scaffold infused with bionutrients that help induce tissue ingrowth. The constructs are implanted under a skin flap in the arm where neovascularization occurs over a period of several months before the implant is grafted in the appropriate location. Scientists have already completed successful trials with this method using murine models and are currently conducting human trials in India and the United Kingdom. Children born with congenital deformities, such as anotia or microtia, continue to be a major concern in third-world countries, such as India, where there is a desperate need for plastic surgeons and facial reconstruction. Over a dozen children have already enlisted in the initial clinic trials taking place in Mumbai. The procedure will hopefully decrease the need for multiple-staged operations and more invasive traditional methods, such as rib cartilage harvesting.

Recent studies out of Korea have also demonstrated the role of 3D printing for use in rhinoplasties.[82] In this study, 3D printed PCL scaffolds were printed and infused with fibrin and chondrocytes. The implant was used as an augmentation material in the nasal dorsum of rabbits. Implants were harvested 3 months postimplantation and evaluated. Implant structural integrity remained intact with minimal inflammatory changes noted on histologic evaluation. Imaging confirmed implant location without any evidence of migration or extrusion. Xu et al[83] also demonstrated similar promising results with the use of 3D bioprinted nasal alar cartilage in mice. These studies further substantiate the feasibility of 3D printed collagen implant development and its use as a biocompatible augmentation material for use in rhinoplasties.

Additional Applications and Manufacturing Advancements

The 3D printed cartilage and collagen implants have multiple applications outside PRS, such as its use in tracheal-bronchial stents, vertebrae, menisci, and knee implants, which have prompted its accelerated advancement in the last several years.[80,84,85] Biocompatible tracheal bronchial stents have been used in multiple occasions on patients with tracheal stenosis and malacias and have demonstrated successful tissue integration and native cellular regeneration.[85–87] Researchers at Feinstein Institute have gone further to produce 3D printed tracheal segments within hours using chondrocyte and collagen based scaffolding that were viable in vitro.[87] These constructs were produced using only a standard commercial 3D printer and modified incubator to act as a bioreactor. This study, among others, has demonstrated that biologic implants have the potential to be made quickly and cheaply with modified readily available commercial equipment.[88,89] Noted speed advancements in collagen implant manufacturing for nose, ear, and knee implants were recently announced by ETH Zürich's Cartilage Engineering and Regeneration laboratory.[90] Researchers developed a process that enabled hospitals to produce full-size nose implants in under 20 minutes.

SKIN

Skin grafting is traditionally indicated for the treatment of major skin defects, due to trauma, burns, or tumor excision, which cannot be closed primarily. Often times, in the cases of extensive burns, there is not enough healthy skin to harvest to cover the defect, or the size of the donor site may compromise adequate cosmetic or functional results. Despite the numerous synthetic and bioengineered skin substitutes currently available, none have provided equivalent results to that of autologous skin grafts.[91–94] Optimal skin substitutes must be durable, prevent water loss, lack antigenicity, resist infection, and conform to irregular wound surfaces.[95,96]

Three-dimensional skin printing provides a potential solution to this issue. The epidermal/dermal layer is much less complex than that of other organs; the planar structure and orientation has lead to more rapid development and application. The use of 3D scanners and printers has enabled researchers to reproduce skin histologic architecture with layer/depth specific cellular deposition. Multiple laboratories have demonstrated the production of viable composite multilayered organomimetic skin models.[97–99] In vivo studies have shown biocompatibility with proliferation of individual cell types.[100] Research using an inkjet approach has demonstrated high-speed construct production, enabling direct deposition of cells into skin defects.[101] The approach has facilitated the deposition of cells with uniform density throughout the volume of the lesion and maintained high cellular viability and function after printing. Histologic layers of skin are maintained through rapid crosslinking of cell containing material via a biocompatible chemical reaction or photoinitiated crosslinking. The technology was shown to be capable of viable skin production for either in vitro or in situ methods.

This alternative approach has been used to deposit bioprinted skin directly into wound or burn defects of mice.[102] Wake Forest School of Medicine is using the technology to print collagen-based skin constructs onto limbs. A scanner is used to determine wound size and depth. Once data are analyzed, the bioprinter distributes a collagen-based substrate composed of specific cell types concordant to the native histologic layer present at that particular skin depth. The project is being funded by the Armed Forces Institute of Regenerative Medicine, which is a US $75 million effort that is being conducted by numerous institutes to develop clinical therapies for tissue regeneration, including skin regeneration for burn injuries. The team plans to eventually manufacture portable machines capable of printing skin directly onto wounds in military settings.[103]

University of Liverpool and University of Manchester are working together on using a high-resolution camera system to process and model printed skin to more accurately match the patient's skin tone and texture. The 3D cameras are able to determine skin geometry taking into account variations, such as wrinkles, veins, and freckles. This allows researchers to reproduce depth variations that often times become more evident in the presence of varying light sources and is influenced by factors, such as shadows. Additionally, the project has begun collecting a database that will include 3D images of several hundred skin type variants. These will be used as templates for use in remote areas or countries without access to calibrated 3D camera systems.[104]

University of Toronto has made major progress with manufacturing speeds by developing a 3D bioprinter that can rapidly create artificial skin grafts from patient cells to help treat extensive burns. The 3D printers are capable of simultaneously printing several successive complex layers consisting of different cell types. The printer produces a hydrogel biopolymer composite using the patient's keratinocytes and fibroblast cells to mimic the epidermal and dermal layers. The biodegradable wound dressing has been able to improve wound healing in mice with compromised immune systems and is currently being tested in porcine skin grafts. Human clinical trials are still about 2 years away.[105]

Researchers have developed a 3D printed fibrin based matrix with cellular-embedded components to assist in wound healing. The portable bioprinter includes a built-in laser scanner that determines wound depth and area. Scan data enable the device to determine appropriate cell layers. The system has successfully printed grafts to treat large skin defects in full thickness skin defect porcine models.[106] Another study used stem cell–derived amniotic fluid to print skin to successfully treat full thickness skin wounds in mice.[101] The hope is to integrate this technology to deliver a porous custom facial neodermis graft that could be directly printed onto the patient.[107]

Additional applications for the technology is also being directed toward using bioprinted skin tissue for drug and product testing, as being seen with new collaborating partners, Organovo biomedical and the L'Oreal group.[108] L'Oreal has been producing a patented skin, called Episkin, from incubated skin cells donated from patients for years. The company has invested over US $1 billion in laboratory grown human skin for research and development in product testing.[109] Organovo, on the other hand, was one of the pioneers for the bioprinting of human tissues, most notable for creating a 3D bioprinted liver system.[110,111] New financial backing and plans for a large commercial scale 3D printing platform will hopefully stimulate skin bioprinting technology to develop more accurate nonanimal-based product testing models as well as further medical applications in burn care.

CONCLUSION

The increasing availability of 3D printing devices and software has now made using the technology technically and economically feasible. Designs often times are made available online and are open source bypassing specialized manufacturing processes, fostering research collaboration, and offering advantages in both cost and time savings. Testable prototypes can be rapidly produced, modified, and reprinted within a day, making it a pivotal tool in translational research.

Applications of 3D bioprinting will most likely be seen first in orthopedic and plastic surgery due to the simpler constructions and near clinical applications of soft tissue and bone implant development compared with that of complex organ production. The biomedical functions of organs, such as the liver and kidney, are still decades away before human application, yet many functional in vitro representations have already been constructed (kidney, liver, vasculature, and so on).[110–116] Unlike these structures which require stratified layering of millions of functioning cells including dozens of cell types, the 3D constructs that are most commonly used in plastic surgery have more basic architecture and function, serving primarily supportive or protective roles.

Three-dimensional printing provides the ability to construct complex individualized implants that not only improve patient outcomes but also increase economic feasibility. The additional complexity of the 3D implant does not increase its manufacturing costs and allows implant utilization to meet the cost realities of the overall health care system.[71] Unlike traditional manufacturing methods, large-scale production is not required to reduce costs with the cost of the first custom-printed 3D implant being as inexpensive as the last. This is especially advantageous in the production of low-volume, highly customized, or complex products.[117]

Readily available designs with low overheads provide a viable alternative to expensive traditional commercial products. Continued development of cheaper manufacturing processes using preexisting printing technology will further lower these costs and may expedite more widespread global adoption. The technology and its products have a potential to provide a level of accessibility that is paramount for remote and resource-limited habitats where biomedical research and health care are most often limited.[118,119] It is in these developing countries and impoverished underserved communities that patients with traumatic injuries have notoriously been unable to receive appropriate reconstruction in the past.[72]

The 3D printing-based technologies will have an immense impact on the reconstruction of traumatic injuries as well as tissue loss associated with significant oncologic resections. In addition to reconstructive procedures, the technology has an achievable potential for breakthroughs in the improvement of facial and limb prosthetic development as well as advancements in biologic and synthetic implants that will provide more natural tactile qualities and appearance for the patient.

REFERENCES

1. McCue T. 3D Printing Stock Bubble? $10.8 Billion By 2021. Forbes. http://www.forbes.com/sites/tjmccue/2013/12/30/3d-printing-stock-bubble-10-8-billion-by-2021/. Accessed June 14, 2015.
2. Bird J. Exploring the 3D printing opportunity. *The Financial Times*. 2012.
3. George A. 3-D Printed Car Is as Strong as Steel, Half the Weight, and Nearing Production. Wired. http://www.wired.com/autopia/2013/02/3d-printed-car/. Accessed February 27 2015.
4. Marks P. 3D printing: The world's first printed plane. New Scientist. http://www.newscientist.com/article/dn20737-3d-printing-the-worlds-first-printed-plane.html#.Ux4SLx_LI7x. Accessed August 01, 2014.
5. Greenberg A. Meet The 'Liberator': Test-Firing The World's First Fully 3D-Printed Gun. Forbes. http://www.forbes.com/sites/andygreenberg/2013/05/05/meet-the-liberator-test-firing-the-worlds-first-fully-3d-printed-gun/. Published May 5, 2013. Accessed June 14, 2015.
6. Macguire E. Dutch architects build world's first 3D printed house. CNN. http://edition.cnn.com/2014/04/13/business/3d-printed-house-amsterdam/. Accessed April 14, 2015.
7. Murphy SV, Atala A. 3D bioprinting of tissues and organs. *Nat Biotechnol*. 2014;32:773–785.
8. Zopf DA, Hollister SJ, Nelson ME, et al. Bioresorbable airway splint created with a three-dimensional printer. *N Engl J Med*. 2013;368:2043–2045.

9. Mannoor MS, Jiang Z, James T, et al. 3D printed bionic ears. *Nano Lett*. 2013; 13:2634–2639.
10. Zein NN, Hanouneh IA, Bishop PD, et al. Three-dimensional print of a liver for preoperative planning in living donor liver transplantation. *Liver Transpl*. 2013; 19:1304–1310.
11. Krassenstein E. 3D Printing Saves the Life of a Newborn with Cloverleaf Skull Syndrome in Brazil. 3dprint.com. http://3dprint.com/48390/cloverleaf-skull-syndrome/. Accessed June 3, 2015.
12. Gerstle TL, Ibrahim AS, Kim PS, et al. A Plastic Surgery Application in Evolution. *Plast Reconstr Surg*. 2014;133:446–451.
13. Watson RA. A low-cost surgical application of additive fabrication. *J Surg Educ*. 2014;71:14–17.
14. Ziegler-Graham K, MacKenzie EJ, Ephraim PL, et al. Estimating the prevalence of limb loss in the United States: 2005 to 2050. *Arch Phys Med Rehabil*. 2008; 89:422–429.
15. Owings M, Kozak LJ. *National Center for Health Statistics. Ambulatory and Inpatient Procedures in the United States, 1996*. Hyattsville, Md.: U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 1998.
16. Robohand News. Robohand.net. http://www.robohand.net/press-package/. Accessed June 3, 2015.
17. Tech-based solutions for disabilities. Not Impossible Foundation. http://notimpossible.com. Accessed June 3, 2015.
18. WHO. Disability and health. World Health Organization. 2014. http://www.who.int/mediacentre/factsheets/fs352/en/. Accessed June 3, 2015.
19. Google. Pursuing transformative technology with the Google Impact Challenge: Disabilities. 2015. http://googleblog.blogspot.com/2015/05/google-impact-challenge-disabilities.html. Accessed June 3, 2015.
20. Harris CM, Laughlin R. Reconstruction of Hard and Soft Tissue Maxillofacial Defects. *Atlas Oral Maxillofac Surg Clin North Am*. 2013;21:127–138.
21. Gentile MA, Tellington AJ, Burke WJ, et al. Management of midface maxillofacial trauma. *Atlas Oral Maxillofac Surg Clin North Am*. 2013;21:69–95.
22. Brydone AS, Meek D, Maclaine S. Bone grafting, orthopaedic biomaterials, and the clinical need for bone engineering. *Proc Inst Mech Eng H*. 2010;224:1329–1343.
23. Hicks J. Peking University Implants First 3D Printed Vertebra. Forbes. http://www.forbes.com/sites/jenniferhicks/2014/08/19/peking-university-implants-first-3d-printed-vertebra/. Published August 19, 2014. Accessed April 15, 2015.
24. Sparks D. 3D Printer Uses CT Scan to Print Out Model of Hip Joint Before Surgery. Mayo Clinic. 2013. http://www.mayoclinic.org/tests-procedures/hip-replacement-surgery/multimedia/vid-20078391. Accessed April 16, 2015.
25. 3D printed hip puts teenager back on her feet. Reuters. 2013. http://www.reuters.com/video/2015/03/21/3d-printed-hip-puts-teenager-back-on-her?videoId=276692685. Accessed April 16, 2015.
26. Beerbohm M. 3-D Printed Pelvis. Orthopedic and Density News, Healthpoint Capital. 2014. http://www.healthpointcapital.com/research/2014/02/12/3d_printed_pelvis/. Accessed April 16, 2015.
27. World's first patient specific jaw implant. Metal Powder Report. http://csmres.co.uk/cs.public.upd/article-downloads/jawProof.pdf. Published April 2012. Accessed April 15, 2015.
28. Medical 4WEB. Over 3,000 4WEB Medical 3D-Printed Orthopedic Truss Implants Used By Surgeons. 2014. http://www.prnewswire.com/news-releases/over-3000-4web-medical-3d-printed-orthopedic-truss-implants-used-by-surgeons-282418411.html. Accessed April 16, 2015.
29. 3D-printed skull implanted in patient. http://www.umcutrecht.nl/en/Research/News/3D-printed-skull-implanted-in-patient. Accessed March 24, 2015.
30. Reichert JC, Cipitria A, Epari DR, et al. A tissue engineering solution for segmental defect regeneration in load-bearing long bones. *Sci Transl Med*. 2012;4:141ra93.
31. Li J, Hsu Y, Luo E, et al. Computer-Aided design and manufacturing and rapid prototyped nanoscale hydroxyapatite/polyamide (n-HA/PA) construction for condylar defect caused by mandibular angle ostectomy. *Aesthetic Plast Surg*. 2011;35:636–640.
32. Li J, Zhang L, Lv S, et al. Fabrication of individual scaffolds based on a patient-specific alveolar bone defect model. *J Biotechnol*. 2011;151:87–93.
33. Cesarano J, Dellinger JG, Saavedra MP, et al. Customization of load-bearing hydroxyapatite lattice scaffolds. *Int J Appl Ceram Technol*. 2005;2:212–220.
34. Lee CH, Marion NW, Hollister S, et al. Tissue formation and vascularization in anatomically shaped human joint condyle ectopically in vivo. *Tissue Eng Part A*. 2009;15:3923–3930.
35. Klammert U, Gbureck U, Vorndran E, et al. 3D powder printed calcium phosphate implants for reconstruction of cranial and maxillofacial defects. *J Craniomaxillofac Surg*. 2010;38:565–570.
36. Wang P, Hu J, Ma PX. The engineering of patient-specific, anatomically shaped, digits. *Biomaterials*. 2009;30:2735–2740.
37. Grayson WL, Frohlich M, Yeager K, et al. Engineering anatomically shaped human bone grafts. *Proc Natl Acad Sci*. 2009;107:3299–3304.
38. Lam CXF, Hutmacher DW, Schantz JT, et al. Evaluation of polycaprolactone scaffold degradation for 6 months in vitro and in vivo. *J Biomed Mater Res A*. 2009;90A:906–919.
39. Woodruff MA, Hutmacher DW. The return of a forgotten polymer—polycaprolactone in the 21st century. *Prog Polym Sci*. 2010;35:1217–1256.
40. Biomedical Devices, OsteoFab Medical Devices and Implants. Oxford Performance Materials. http://www.oxfordpm.com/biomedical_parts.php. Accessed March 24, 2015.
41. Temple JP, Hutton DL, Hung BP, et al. Engineering anatomically shaped vascularized bone grafts with hASCs and 3D-printed PCL scaffolds. *J Biomed Mater Res A*. 2014;102:4317–4325.
42. Grayson WL, Chao PH, Marolt D, et al. Engineering custom-designed osteochondral tissue grafts. *Trends Biotechnol*. 2008;26:181–189.
43. Tarafder S, Bose S. Polycaprolactone-coated 3D printed tricalcium phosphate scaffolds for bone tissue engineering: in vitro alendronate release behavior and local delivery effect on in vivo osteogenesis. *ACS Appl Mater Interfaces*. 2014; 6:9955–9965.
44. Bose S, Vahabzadeh S, Bandyopadhyay A. Bone tissue engineering using 3D printing. *Mater Today*. 2013;16:496–504.
45. Fielding G, Bose S. SiO_2 and ZnO dopants in three-dimensionally printed tricalcium phosphate bone tissue engineering scaffolds enhance osteogenesis and angiogenesis in vivo. *Acta Biomater*. 2013;9:9137–9148.
46. Tarafder S, Davies NM, Bandyopadhyay A, et al. 3D printed tricalcium phosphate bone tissue engineering scaffolds: effect of SrO and MgO doping on in vivo osteogenesis in a rat distal femoral defect model. *Biomater Sci*. 2013;1:1250–1259.
47. De Coppi P, Bartsch G, Siddiqui MM, et al. Isolation of amniotic stem cell lines with potential for therapy. *Nat Biotechnol*. 2007;25:100–106.
48. Inzana JA, Olvera D, Fuller SM, et al. 3D printing of composite calcium phosphate and collagen scaffolds for bone regeneration. *Biomaterials*. 2014;35:4026–4034.
49. Product information: 3D organomimetic models for tissue engineering. *Biotechnol J*. 2013;8:283.
50. Petrochenko PE, Torgersen J, Gruber P, et al. Laser 3D printing with sub-microscale resolution of porous elastomeric scaffolds for supporting human bone stem cells. *Adv Healthc Mater*. 2015;4:739–747.
51. Pati F, Song TH, Rijal G, et al. Ornamenting 3D printed scaffolds with cell-laid extracellular matrix for bone tissue regeneration. *Biomaterials*. 2015;37:230–241.
52. Castilho M, Moseke C, Ewald A, et al. Direct 3D powder printing of biphasic calcium phosphate scaffolds for substitution of complex bone defects. *Biofabrication*. 2014;6:015006.
53. O'Connell RL, Stevens RJ, Harris PA, et al. Review of three-dimensional (3D) surface imaging for oncoplastic, reconstructive and aesthetic breast surgery. *Breast*. 2015;24:331–342.
54. Chae MP, Hunter-Smith DJ, Spychal RT, et al. 3D volumetric analysis for planning breast reconstructive surgery. *Breast Cancer Res Treat*. 2014;146:457–460.
55. Henseler H, Smith J, Bowman A, et al. Subjective versus objective assessment of breast reconstruction. *J Plast Reconstr Aesthet Surg*. 2013;66:634–639.
56. Xi W, Perdanasari AT, Ong Y, et al. Objective breast volume, shape and surface area assessment: a systematic review of breast measurement methods. *Aesthetic Plast Surg*. 2014;38:1116–1130.
57. Pacifico MD, See MS, Cavale N, et al. Preoperative planning for DIEP breast reconstruction: early experience of the use of computerised tomography angiography with VoNavix 3D software for perforator navigation. *J Plast Reconstr Aesthet Surg*. 2009;62:1464–1469.
58. DeLuca-Pytell D, Piazza R, Holding J, et al. *The incidence of tuberous breast deformity in asymmetric and symmetric mammaplasty patients. In: Breast Augmentation: Principles and Practice*. Germany: Springer-Verlag Berlin and Heidelberg GmbH & Co. K; 2009.
59. Rohrich RJ, Hartley W, Brown S. Incidence of breast and chest wall asymmetry in breast augmentation: a retrospective analysis of 100 patients. *Plast Reconstr Surg*. 2006;118;(7 suppl):7S–13S.
60. Khan UD. Breast and chest asymmetries: classification and relative distribution of common asymmetries in patients requesting augmentation mammoplasty. *Eur J Plast Surg*. 2010;34:375–385.
61. Tenna S, Cogliandro A, Cagli B, et al. Breast hypertrophy and asymmetry: a retrospective study on a sample of 344 consecutive patients. *Acta Chir Plast*. 2012; 54:9–12.
62. Grewal NS, Fisher J. Why do patients seek revisionary breast surgery? *Aesthet Surg J*. 2013;33:237–244.
63. Hvilsom GB, Hölmich LR, Henriksen TF, et al. Local complications after cosmetic breast augmentation: results from the Danish Registry for Plastic Surgery of the breast. *Plast Reconstr Surg*. 2009;124:919–925.

64. Rengier F, Mehndiratta A. 3D printing based on imaging data: review of medical applications. *Int J Comput Assist Radiol Surg*. 2010;5:335–341.
65. Whitehead N. 3-D Tissue Printing Will Help Women with Breast Cancer. Website. http://news.utep.edu/?p=8183. March 11, 2014. Accessed March 16, 2015.
66. Evans KK, Rasko Y, Lenert J, et al. The use of calcium hydroxylapatite for nipple projection after failed nipple-areolar reconstruction. *Ann Plast Surg*. 2005;55: 25–29.
67. Yanez M, Rincon J, Cortez P, et al. Printable cellular scaffold using self-crosslinking agents. *J Imaging Sci Technol*. 2012;56:1–5.
68. Bita N. Absolutely bio-fabulous: 'bioprinting' to regrow damaged body parts. *Australian*. 2014.
69. Reisberg DJ, Habakuk SW. A history of facial and ocular prosthetics. *Adv Ophthalmic Plast Reconstr Surg*. 1990;8:11–24.
70. 3-D Printed Facial Prosthesis Offers New Hope for Eye Cancer Patients Following Surgery. American Academy of Ophthalmology. http://www.aao.org/news-room/news-releases/detail/3d-printed-facial-prosthesis-offers-new-hope-eye-c. Accessed May 10, 2015.
71. Schubert C, van Langeveld MC, Donoso LA. Innovations in 3D printing: a 3D overview from optics to organs. *Br J Ophthalmol*. 2014;98:159–161.
72. Banks J. Adding value in additive manufacturing: researchers in the United Kingdom and Europe look to 3D printing for customization. *IEEE Pulse*. 2013;4:22–26.
73. He Y, Xue GH, Fu JZ. Fabrication of low cost soft tissue prostheses with the desktop 3D printer. *Sci Rep*. 2014;4:6973.
74. Soft tissue additive manufacturing. The University of Sheffield. http://www.shef.ac.uk/research/impact/magazine/additiveman. Accessed May 10, 2015.
75. Erickson B, Chao D, Grace L, et al. Rapid and cost-effective orbital prosthesis fabrication via automated non-contact facial topography mapping and 3-D printing. *Am Soc Opththalmic Plast Reconstruct Surg*. 2014.
76. Reiffel AJ, Kafka C, Hernandez KA, et al. High-fidelity tissue engineering of patient-specific auricles for reconstruction of pediatric microtia and other auricular deformities. *PLoS One*. 2013;8:e56506.
77. Markstedt K, Mantas A, Tournier I, et al. 3D Bioprinting human chondrocytes with nanocellulose-alginate bioink for cartilage tissue engineering applications. *Biomacromolecules*. 2015;16:1489–1496.
78. Xu T, Binder KW, Albanna MZ, et al. Hybrid printing of mechanically and biologically improved constructs for cartilage tissue engineering applications. *Biofabrication*. 2012;5:015001.
79. Visser J, Melchels FP, Jeon JE, et al. Reinforcement of hydrogels using three-dimensionally printed microfibres. *Nat Commun*. 2015;6:6933.
80. Lee CH, Rodeo SA, Fortier LA, et al. Protein-releasing polymeric scaffolds induce fibrochondrocytic differentiation of endogenous cells for knee meniscus regeneration in sheep. *Sci Transl Med*. 2014;6:266ra171.
81. Knapton S. Children to be implanted with 3D printed ears. The Telegraph. http://www.telegraph.co.uk/news/science/science-news/11141971/Children-to-be-implanted-with-3D-printed-ears.html. Published October 6, 2014. Accessed May 13, 2015.
82. Kim YS, Shin YS, Park do Y, et al. The application of three-dimensional printing in animal model of augmentation rhinoplasty. *Ann Biomed Eng*. 2015;43:2153–2162.
83. Xu Y, Fan F, Kang N, et al. Tissue Engineering of Human Nasal Alar Cartilage Precisely by Using Three-Dimensional Printing. *Plast Reconstr Surg*. 2015; 135:451–458.
84. Jungebluth P, Alici E, Baiguera S, et al. Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. *Lancet*. 2011;378:1997–2004.
85. Hornick J. 3D printing and the future (or demise) of intellectual property. *3D Printing*. 2014;1:14–23.
86. Chang JW, Park SA, Park JK, et al. Tissue-engineered tracheal reconstruction using three-dimensionally printed artificial tracheal graft: preliminary report. *Artif Organs*. 2014;38:E95–E105.
87. Shin YS, Choi JW, Park JK, et al. Tissue-engineered tracheal reconstruction using mesenchymal stem cells seeded on a porcine cartilage powder scaffold. *Ann Biomed Eng*. 2015;43:1003–1013.
88. Feinstein Institute for Medical Research Create Cartilage to Repair Tracheal Damage with 3D Printing. 2015. http://www.feinsteininstitute.org/2015/01/using-3d-printing-makerbot-feinstein-institute-medical-research-create-cartilage-repair-tracheal-damage/. Accessed April 4, 2015.
89. Drescher P, Spath S, Seitz H. Fabrication of biodegradable, porous scaffolds using a low-cost 3D printer. *Int J Rapid Manufacturing*. 2014;4.
90. Zenobi-Wong M. ETH—cartridge engineering and regeneration laboratory. http://www.cartilage.ethz.ch. Accessed March 31, 2015.
91. Debels H, Hamdi M, Abberton K, et al. Dermal matrices and bioengineered skin substitutes. *Plast Reconstr Surg Glob Open*. 2015;3:e284.
92. Halim AS, Khoo TL, Mohd Yussof SJ. Biologic and synthetic skin substitutes: an overview. *Indian J Plast Surg*. 2010;43:S23–S28.
93. Nathoo R, Howe N, Cohen G. Skin substitutes: an overview of the key players in wound management. *J Clin Aesthet Dermatol*. 2014;7:44–48.
94. Sun BK, Siprashvili Z, Khavari PA. Advances in skin grafting and treatment of cutaneous wounds. *Science*. 2014;346:941–945.
95. Shores JT, Gabriel A, Gupta S. Skin substitutes and alternatives: a review. *Adv Skin Wound Care*. 2007;20:493–508.
96. Sheridan RL, Moreno C. Skin substitutes in burns. *Burns*. 2001;27:92.
97. Rimann M, Graf-Hausner U. Synthetic 3D multicellular systems for drug development. *Curr Opin Biotechnol*. 2012;23:803–809.
98. Lee W, Debasitis JC, Lee VK, et al. Multi-layered culture of human skin fibroblasts and keratinocytes through three-dimensional freeform fabrication. *Biomaterials*. 2009;30:1587–1595.
99. Milkert H. Qingdao Unique to Begin Animal Testing on 3D Printed Skin within the Year. 3D Printing—Health. http://3dprint.com/53562/3d-printed-skin-corneas/. Accessed May 21, 2015.
100. Rimann M, Bleisch M, Kuster M, et al. Organomimetic skin model production based on novel bioprinting technology. *CTI Medtech Event*. 2011.
101. Skardal A, Mack D, Kapetanovic E, et al. Bioprinted amniotic fluid-derived stem cells accelerate healing of large skin wounds. *Stem Cells Transl Med*. 2012;1: 792–802.
102. Keriquel V, Guillemot F, Arnault I, et al. In vivo bioprinting for computer- and robotic-assisted medical intervention: preliminary study in mice. *Biofabrication*. 2010;2:014101.
103. Printing Skin Cells on Burn Wounds. Wake Forest School of Medicine. 2015. http://www.wakehealth.edu/Research/WFIRM/Research/Military-Applications/Printing-Skin-Cells-On-Burn-Wounds.htm. Accessed May 21, 2015.
104. Trafford S. Developing convincing 3D printed skin. University of Liverpool. 2013. http://news.liv.ac.uk/2013/11/27/developing-convincing-3d-printed-skin/. Accessed May 21, 2015.
105. Thakur G, Prashanthi K, Thundat T. Directed self-assembly of proteins into discrete radial patterns. *Sci Rep*. 2013;3:1923.
106. Edwards L. 3D bio-printers to print skin and body parts. http://phys.org/news/2011-02-3d-bio-printers-skin-body.html. Accessed June 14, 2015.
107. Cheng X, Yoo JJ, Hale RG. Biomask for skin regeneration. *Regen Med*. 2014;9: 245–248.
108. L'Oreal USA Announces Research Partnership with Organovo to Develop 3-D Bioprinted Skin Tissue. Organovo. 2015. http://ir.organovo.com/news/press-releases/press-releases-details/2015/LOreal-USA-Announces-Research-Partnership-with-Organovo-to-Develop-3-D-Bioprinted-Skin-Tissue/default.aspx?_ga=1.5986035.1973647837.1432236034. Accessed May 21, 2015.
109. Rhodes M. Inside L'Oreal's Plan to 3-D Print Human Skin. Wired.com. 2015. http://www.wired.com/2015/05/inside-loreals-plan-3-d-print-human-skin/. Accessed May 31, 2015.
110. Robbins J, O'Neil C, Gorgen V, et al. Bioprinted three-dimensional (3D) human liver constructs provide a model for interrogating liver biology. *Am Soc Biol*. 2013.
111. The Importance of Multicellularity in Liver Homeostasis and Injury and Functional Stability of exVive3DTM Liver, Bioprinted Human Tissues. Organovo Publications. http://www.organovo.com/science-technology/publications. Accessed May 24, 2015.
112. King S, Creasey O, Presnell S, et al. Design and characterization of a multicellular, three-dimensional (3D) tissue model of the human kidney proximal tubule. *Exp Biol*. 2015.
113. Bullis K. EmTech: 3-D Printing Complex Kidney Components. MIT Technology Review. 2014. http://www.technologyreview.com/news/531106/emtech-3-d-printing-complex-kidney-components/. Accessed May 24, 2015.
114. Harmon C. Use for 3-D Printers: Creating Internal Blood Vessels for Kidneys, Livers, Other Large Organs. Scientific American. http://www.scientificamerican.com/article/new-use-3d-printing-blood-vessel-creation-kidney-liver-large-organs/. Accessed May 24, 2015.
115. Hoch E, Tovar GE, Borchers K. Bioprinting of artificial blood vessels: current approaches towards a demanding goal. *Eur J Cardiothorac Surg*. 2014;46: 767–778.
116. Bertassoni LE, Cecconi M, Manoharan V, et al. Hydrogel bioprinted microchannel networks for vascularization of tissue engineering constructs. *Lab Chip*. 2014;14: 2202–2211.
117. Mertz L. Dream it, design it, print it in 3-D: what can 3-D printing do for you? *IEEE Pulse*. 2013;4:15–21.
118. Rankin TM, Giovinco NA, Cucher DJ, et al. Three-dimensional printing surgical instruments: are we there yet? *J Surg Res*. 2014;189:193–197.
119. Lang T. Advancing global health research through digital technology and sharing data. *Science*. 2011;331:714–717.