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Clinical Applications of 3D Printing: Primer for Radiologists

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Abstract

3-dimensional (3D) printing refers to a number of manufacturing technologies that create physical models from digital information. Radiology is poised to advance the application of 3D printing in healthcare because our specialty has an established history of acquiring and managing the digital information needed to create such models. The 3D Printing Task Force of the Radiology Research Alliance presents a review of the clinical applications of this burgeoning technology with a focus on the opportunities for radiology. Topics include uses for treatment planning, medical education and procedural simulation, as well as patient education. Challenges for creating custom implantable devices including financial and regulatory processes for clinical application are reviewed. Precedent procedures that may translate to this new technology are discussed. The task force identifies research opportunities needed to document the value of 3D printing as it relates to patient care.

Keywords

3D printing; Three-dimensional printing; Personalized medicine; Additive manufacturing; Radiology; Preoperative planning

Introduction

What began as a largely industrial tool to facilitate concept-to-prototype development 3D printing has evolved into a widely used technology, affecting many aspects of modern society. The term “3D printing” grew out of the research and development labs of the automotive and aerospace industries (1). The technology was developed throughout the 1980s and 1990s (2 – 5) and medical applications were initially reported in the early 2000s (6 - 9). Initially, these reports focused on custom prostheses (6, 7) but as the technology improved, reports of using anatomic models for preoperative planning began appearing (10-13). Today, 3D printing continues to find new applications: customized eyeglasses can be printed to exact specifications (14), an increasing number of foods can be printed on demand (15), and there are plans to manufacture cars entirely using 3D printing (16).

Recent rapid growth of 3D printing both in medicine has been staggering. A search of Pubmed.gov using the term “3D printing” yielded only 6 publications in the year 2000, 61 publications in 2010, and over 1,100 publications in 2016. To encourage continued growth of this technology, the National Additive Manufacturing Innovation Institute was launched in 2012 (17). Many professional societies have also advocated the use of this technology in medicine. For example, the Society for Manufacturing Engineers has a dedicated medical 3D printing workgroup (18). In 2016, the Radiological Society of North America (RSNA) formed the 3D Printing Special Interest Group (SIG). The 3D Printing SIG has already sponsored many educational sessions at the annual meeting and is committed to building evidence for clinical utility of 3D printing (19).

Undoubtedly this topic has gained popularity because of the tremendous potential it offers to radiologists, our colleagues, and patients. If implemented correctly, 3D printing promises to improve patient care and enhance the relative contribution to that care by radiologists. Specifically, 3D printing can deliver personalized medicine based on the anatomic data radiologists acquire and interpret every day. Providing such a service offers a new way to interact with referring clinicians and a potential way radiology can demonstrate value in patient care.

Radiologists have witnessed the evolution of medical imaging that allows for 3D printing. Multiplanar imaging with CT and MRI gave rise to 3D reconstructions that improved the evaluation of complex anatomy (20-22). At its most basic level, 3D printing takes imaging data from the two dimensions of a computer screen to the three dimensions of the real world (22).

3D printing has been used in a wide range of health care settings including: Cardiology (23), Cardiothoracic Surgery (24), Critical Care (25), Gastroenterology (26), General Surgery (27), Interventional Radiology (28), Neurosurgery (29, 30), Ophthalmology (31), Oral and Maxillofacial Surgery (32, 33), Orthopedic Surgery (34), Otolaryngology (35, 36), Plastic Surgery (37), Podiatry (38), Pulmonology (39), Radiation Oncology (40), Transplant Surgery (41), Urology (42), and Vascular surgery (43).

The most immediate clinical applications of 3D printing are for pre-surgical planning, intra-operative guidance, and the production of custom implants. Increasingly, 3D printed models are also used for educating physicians, trainees, and patients. However, clinical implementation of 3D printing has already faced important challenges, including financial, regulatory, and medicolegal restrictions. Discussed in subsequent sections, 3D printing has faced some challenges including lack of reimbursement as well as the initial time, cost, and personnel required to start a medical 3D printing lab. As advances in 3D printing continue to change health care delivery, what role will the radiology community play?

This article by the 3D Printing Task Force of the Radiology Research Alliance reviews current issues related to the clinical application of 3D printing and their implications for radiologists. Specific topics include treatment planning using 3D printing, customized prostheses, bioprinting, 3D printing for medical and patient education, challenges to the clinical application of 3D printing, and opportunities for radiologists. As more surgeons employ 3D printing technologies for treatment planning, it is important for radiologists to learn about the field and stay abreast of advancements. Since radiologists are responsible for proper image acquisition and interpretation of medical images, which are used to generate 3D printed models, radiologists have an opportunity to take the lead in this emerging field and through 3D printing can participate more directly in operative planning and patient care.

Transforming Clinical Care

Treatment Planning—Treatment planning is a multistep process where clinical and imaging information are integrated to determine the best therapeutic options while saving operative time. With 3D printing, this can be creation of haptic models to plan the surgical approach along with cross-sectional imaging or, alternatively, creating custom prosthetics based on patient-specific anatomy. For over a decade, additive manufacturing techniques have been used to improve surgical planning. Orthopedic, Maxillofacial, and Cardiothoracic surgeons were among the first to use 3D printing techniques to design custom prosthetics (25, 33, 34).

Why are 3D models of patient-specific anatomy so useful for operative planning? Perhaps the most obvious answer is that the models provide surgeons with an opportunity to understand the complex anatomy unique to each case in the dimension they will be operating in (28) (Figure 1). These 3D printed anatomic models based on patient-specific anatomy can be used for surgical planning both in and out of the operating room (44). The use of 3D printing for treatment planning is subsequently discussed in three sections: Fracture Fixation, Resection of Renal Tumors, and Cardiovascular Applications.

Fracture Fixation: The use of 3D printed models for operative planning has been implemented in a number of orthopedic and fracture fixation applications (34, 45) (Figure 2). For example, Mao et al. (46) used 3D models in 22 patients with hip arthroplasty requiring revision surgery. The 3D models were used to fit the surgically altered acetabulum with commercially available cages or custom acetabular cages.

Chung et al. (47) used 3D printed calcaneal models in patients with intra-articular fractures to plan internal fixation and plating. Preoperatively, the models were used to determine an appropriate approach for fracture reduction. In some patients, the models were also sterilized and used intraoperatively. Huang et al. (48) used 3D printing to plan screw trajectories prior to internal fixation of tibial plateau fractures. Pacione et al. (49) reported on a case of a complex deformity of the skull base requiring surgery. The 3D model of the skull base and upper cervical spine was used preoperatively to plan the surgical approach and then placed on a stand in the operating room to help guide surgery.

In complex fractures, 3D modeling allows surgeons to preoperatively mold malleable plates to the configuration of the fracture, reducing operative time and costs, and ultimately improving outcomes (50). For example, reconstruction of tibial plateau fractures often requires the use of expensive bone graft material. 3D modeling has the potential for determining the type and quantity of graft material, reducing operative time and the amount of graft material prepared for surgery (27, 34-36).

Resection of Renal Tumors: 3D printing of anatomic models for preoperative planning has been used in planning the surgical approach for the resection of renal tumors. Silberstein et al. (51) used 3D printed models of suspected renal tumors for both pre- and intraoperative guidance. The patients underwent partial nephrectomy, with the urologists finding the models useful in assessing tumor resection margin in relation to the hilar vessels and the collecting system. Wake et al. (52) retrospectively identified 10 renal cancers that were characterized with MR prior to resection and fashioned 3D printed models based on T1-weighted post-contrast fat-suppressed gradient-echo sequences. Using these models, they conducted a faux preoperative planning session (the session was conducted after the patients underwent surgery) with three urologists both with imaging alone then subsequently with the 3D printed model and imaging. They administered a questionnaire concerning the surgical approach and understanding of the tumor's anatomy (relationship with the native kidney). When compared to the initial session without the 3D printed model, the session that incorporated both the model and imaging data led to a change in at least one aspect of the surgical approach in all 10 patients. Although these models were not used in the actual planning, the surveyed surgeons did report increased confidence in their understanding of the tumor’s anatomy.

Cardiovascular Applications: 3D printed heart and aortic models have been used for treatment planning in both cardiothoracic surgery and percutaneous cardiology applications. In cardiothoracic surgery, 3D printed anatomic models have been used intraoperatively to help guide the surgical approach, to perform the resection, and to guide tissue reconstruction. Pepper et al. (53) reported on a cohort of 34 patients with Marfan's syndrome who had surgically implemented aortic root support from 3D printed models. From preoperative CT and MR data, personalized aortic roots were manufactured along with an externalized mesh atop of the model. This conglomeration was sterilized and used intraoperatively with good technical success. The 3D printed contours were crucial in ensuring a proper fit and providing a surface for cutting branching points for branch arteries. Hossien et al. (54) used 3D printing in patients with aortic dissections to help determine treatment: open surgery versus endovascular intervention. After surgery, 3D printing can be used to help follow patients’ progress. For example, 3D printed heart model derived from cardiac CT has been used to evaluate the integration of an atrial septal defect occlusion device (55).

Customized Surgical Tools and Prostheses

In addition to its use in the manufacturing of anatomic models, 3D printing can be used for manufacturing custom implants, procedural/operative instruments, and prostheses. Implants and procedural devices, take advantage of the customizability, manufacturing capabilities, and potential low cost of additive manufacturing techniques. 3D printing not only allows implants and procedural tools to be tailored to patient-specific anatomy, it allows products to be manufactured with bland or drug-impregnated materials (56-59). 3D printed biologically active implants are discussed in the Bioprinting Revolution section.

Surgical Tools—Additive manufacturing techniques have been used to fabricate basic surgical instruments and have the potential to reduce cost. For example, Rankin et al. (60) used 3D printing to construct an Army/Navy retractor from polylactic acid based on the designs of the traditional stainless steel model. Although the construct warped and fractured at high tensile strengths, the force was below that used in the operating room. Importantly, each model cost less than $1.00 to manufacture. Fuller et al. (61) described their experience with a prototype of a bone reduction clamp for use in hand surgery. The clamp would require less operative exposure and allow for a more kinetically feasible fracture reduction. Using the services of a commercial 3D printing company, and following creation of a series of plastic prototypes, a stainless steel custom 3D printed clamp was created. The clamp was sterilizable and reusable and was successfully used intraoperatively. The cost of the 6 prototypes and the final stainless steel clam was less than $2,000. This example shows how 3D technology allows for innovation and rapid prototyping, from concept to final product.

Prostheses—Prostheses that are based on patient anatomy are especially useful, taking full advantage of the modeling capabilities of 3D printing. For years, many prostheses have been manufactured in a limited number of sizes. While reducing the cost, such an approach has disadvantages, including reduced patient comfort and reduced lifespan of the hardware. Consequences of an improperly fitted prosthesis include patient embarrassment, reduced patient comfort and compliance, even depression (62, 63).

Customized prostheses overcome many of the disadvantages of conventional devices. While customized prostheses manufactured without 3D printing are available, they come at a much higher cost. With 3D printing, the costs of customized prosthesis have been reduced significantly. More importantly, 3D printed prostheses often have a better “fit”, tailored to the individual needs of the patient. In radiation oncology, 3D printed custom vaginal cylinders have been used for targeted vaginal brachytherapy (64-66).

Many 3D printed prostheses have already been FDA approved, including: hearing aids, dental crowns, bone tether plates, skull plates, hip cups, spinal cages, knee trays, facial implants, screws, surgical instruments, and Invisalign® braces (67).

Maxillofacial Prostheses: The use of custom implants for dental and maxillofacial reconstructions is already widely accepted (45). 3D printed implants are used for reconstructions of the temporal bone (including middle ear ossicles), zygomatic bones, calvarial bones, and mandibles (68). These are especially useful following tumor resection or trauma surgery. 3D printed implants have also been used in soft tissues reconstructions of the head and neck, including auricular tissues. Mandibular tumors such as ameloblastomas often require significant bone and soft tissue reconstruction following tumor resection. The use of 3D implants has helped reduce the cosmetic deformities associated with such surgeries (69).

Joint Prostheses: 3D printing has been used for construction of custom joint prostheses. In addition to increased patient comfort, such prostheses have an increased lifespan compared to conventional arthroplasty (70). Although standard implants are available in many sizes, some patients fall outside the commonly available size range. Patients with primary bone tumors or metastatic disease often require modular implants designed to replace the large surgical defect, with marked variability in the design needed for adequate reconstruction.

Open source software and online repositories with prosthetic templates have given patients the ability to print and assemble their own prosthetic, if they purchase the materials and own a 3D printer. Cost of a printer and technical fees for a commercial 3D printing service notwithstanding, estimates of printing an upper extremity prosthetic using 3D print range from $25 to $150 (cost of the materials), compared to several thousand dollars for commercial prosthetics. Polylactic acid and acrylonitrile butadiene styrene are two thermoplastics commonly used in 3D printing of extremity prosthetics, anatomic models, and other 3D printed constructs. Such prostheses 3D printed by patients using open source repositories are not monitored by the health care providers and are thus not subject to federal regulations (71). In contrast, prosthetics produced or prescribed by the health care providers are subject to regulations as they are considered a ‘medical device’ (72). Regulatory aspects of 3D printed constructs are discussed more fully in the ‘Regulatory Challenges’ section.

Conventional 3D manufacturing can be used to develop custom prostheses using any number of materials; even more exciting is the potential for manufacturing customized prostheses that use the patient’s own cell lines grown into a 3D scaffold. This technique is known as “bioprinting” and is discussed in the “Bioprinting Revolution” section.

Patient Education

Increasingly, patients are using the internet to investigate their symptoms and diagnoses (73). Current emphasis on patient centered care makes patient education a top priority for most health care providers. However, communicating imaging reports verbally or by showing patients their CT or MR studies may not be effective, as patients may not understand the two dimensional representation of three dimensional anatomy. Radiologists may improve communication with patients, either by showing the anatomic model directly to the patient or by providing the referring clinicians with the models to be used with patients. Studies have shown that 3D models can be useful in helping patients better understand their medical conditions (74-77). Radiologists should embrace this trend and seek ways to improve our communication with patients, whether by communicating directly with the patient or by providing the referring clinicians with anatomic models. In radiology, 3D anatomic models could be especially useful for explaining imaging findings that many patients have difficulty conceptualizing, such as breast calcifications or fetal anomalies. 3D models can also be used during informed consent for procedures to better demonstrate what will be done during an image-guided procedure. Ultimately, 3D models can help radiologists be more effective communicators and thus increase patient satisfaction. This may be particularly relevant if the patient is being considered for surgery and the anatomic model is used for preoperative planning.

In a study by Bernhard et al. (75), multiphase renal CTs were used to print 3D patient-specific models to supplement patient education. Patients showed significantly greater understanding of their disease, renal anatomy, and the planned surgical procedure. In another study (77) cardiologists used 3D printed models of congenital heart defects derived from cardiac MRs to supplement education of parents. Although the visits were significantly longer, the 3D models were useful for communicating with parents about their child’s disease process, cardiac anatomy, and expected disease course. Tominaga et al. (76) used 3D printing to create stoma models to facilitate training of ostomy care. 3D printed custom models were used to help patients practice cutting the faceplate for their ostomy appliance.

Transforming Medical Education

In addition to improving clinical care, 3D printing has also helped improve medical education.

Anatomy Teaching—Medical schools are beginning to use 3D anatomic models to supplement cadaveric dissection for anatomy education. Trace et al. (78) summarize the benefits of 3D prints for anatomy teaching: 1) models are reproducible and safe to handle, 2) models can be created from a wide variety of imaging sources representing normal and pathologic anatomy. Another benefit is that institutions with fewer resources can share 3D models among institutions.

Such anatomic models of specific sections can be constructed using CT scans of prosected specimens and 3D printing these as life-sized, upscaled, or downscaled models. Printing high resolution can be achieved with fused deposition modeling techniques and usually requires more expensive printer models to achieve sufficient detail. 3D printers that have the capability to print with different densities and colors can be used to accentuate anatomic detail (79).

3D printed anatomic models based on cadaver prosections allows for high detail models, such as ophthalmologic anatomy (79, 80), and have been used to educate medical students. Lim et al. (81) randomized a group of 52 first year medical students to learn external cardiac anatomy using 3D printed models, prosecuted hearts, or a combination of both approaches. They found that the 3D printing-only group performed significantly better on a post-test compared to the other two groups.

There are some limitations in using 3D printing for graduate medical education. Fine detail (small nerve braches and microstructure) often explored in cadaveric subjects can be difficult to replicate with affordable 3D printing techniques. However, the materials used for 3D printing have been expanding to include plastic polymers with various density and rigidity. These material attributes can be used to create better simulations of varied tissue types. For example, using commercial proprietary plastics of different densities, dual material 3D models use different materials to differentiate bone from cartilage (82).

Operative Rehearsal—3D printed anatomic models have been used for virtual surgical planning or surgical simulation and other procedural training for medical students, residents, fellows, and faculty (72, 83). 3D models help simulate specific anatomy and indemnify trainees in a non-stress environment. Importantly, the models allow various surgical approaches to be practiced without harming the patient (75). Soft tissues can be mapped and reconstructed, effectively moving important decisions from the time-constrained operating room to the preoperative setting (84-89) (Figure 3). Weinstock et al. (30) reported a 30 minute reduction in operative time with pre-procedure 3D modeling of pediatric cerebral vascular malformations. Hermsen et al. (90) used 3D printed hearts fabricated from cardiac CTs to perform a surgical simulation of a septal myectomy in patients with hypertrophic cardiomyopathy. The study reported similar myectomy volumes between the resected 3D models and the surgical specimens.

Yoo et al. (83) conducted surgical simulations using 3D printed congenital heart models and hosted a course at several cardiothoracic surgery conferences. Of the 50 attending surgeons and trainees who responded to a post-course survey, all (100%) responders found the course helpful and stated that they would consider using such 3D printed surgical simulations at their institutions. Wilasrusmee et al. (12) reported a case series using 3D anatomic modeling for aorta aneurysm repair planning showed residents at all stages of training were more likely to assess patients in a concordant fashion after reviewing the models.

3D modeling has also been used to optimize treatment strategies based on physiologic properties. Wang et al. (91) used a 3D microfluidic model of a coronary stenosis to determine the best implantation strategy for stenting. The anatomic model allowed detection of areas of low wall shear stress with different stent placements to prevent early stent restenosis.

Other reports have used 3D models for operative rehearsal of cerebrovascular aneurysm repairs (92), transapical aortic valve repairs (93), nephrolithotomy (13), and fiberoptic bronchoscopy (94).

Applications in Radiology—Because medical 3D printing is fundamentally image-centered – creating patient-specific anatomic models, implants, and constructs typically requires CT and MR imaging – the radiologist should play a central role in 3D printing. Ensuring accurate segmentation and transformation of DICOM data to 3D printing compatible files can become a routine part of radiologist’s workflow, especially if 3D printing becomes a billable service. Although other health care providers, radiology technologists, or engineers may have sufficient training to provide accurate segmentations in most cases, radiologists can provide additional expertise in dealing with imaging artifacts such as MR pulsation artifacts and flow voids. In radiology departments, anatomically correct 3D models can be used for procedural practice, such as US guided biopsies. Trainees can practice hand-eye coordination required for image-guided biopsies. As multi-material prints become more available, the fidelity of the models will improve and trainees will also be able to practice optimizing image quality and positioning.

Another potential application of 3D printing in radiology is in the design and manufacture of imaging phantoms. Anatomically correct phantoms can be used in determining the effectiveness of new imaging techniques (95). For example, phantoms used in cardiac imaging can help validate the accuracy of CT calcium scoring and determine the need for correction factors when using different reconstruction algorithms (96).

3D printed phantoms offer low-cost alternatives to commercial phantoms and patient-specific customizability compared to low cost ad hoc phantoms made on site. For example, Mitsouras et al. (97) developed a 3D printed cervical spine MR phantom modeled after a patient with a C7 osteoid osteoma. The investigators performed a simulated MR-guided cryoablation on the phantom and retrospectively compared it to the patient’s actual procedure, finding similar signal and imaging characteristics. Rapid prototyping of such phantoms may be helping in planning and rehearsing image-guided procedures.

Finally, 3D modeling and rapid prototyping has the potential to change the practice of forensic radiology. In the courtroom, virtual models and 3D prints are used to demonstrate various anatomic abnormalities that may be difficult for jury members to understand using cross sectional imaging. 3D models have also been used to reconstruct the crime scene, perform simulations, and preserve evidence. These models have been well received by juries who prefer them over often shocking crime scene or autopsy photographs (98-100).

Research Directions

Bioprinting Revolution—Bioprinting involves the use of various techniques, such as fused deposition modeling, to print bioactive scaffolds impregnated with growth factors designed to stimulate regeneration or drugs that concentrate their activity in the microenvironment, print customized bioactive implants and devices on demand, even generate customized living tissues (56-59, 101, 102).

Bioprinting can also be used for localized drug delivery, limiting or completely eliminating systemic toxicity. The FDA has already approved a 3D printed oral form of levetiracetam (103). Drug-eluted 3D printed constructs under investigation include cutaneous delivery of salicylic acid for acne and antibiotic-impregnated surgical implants (56-58, 104) (Figure 4).

Drug-impregnated 3D printed constructs may offer a superior extended release profile compared to currently available implants with a superficial drug-eluting coating. This design advantage includes a ‘honeycomb’ lattice that increases available surface area for drug impregnation and a layer-by-layer degradation of bioabsorbable plastics; when the superficial layers degrade, new bioactive layers become available (56, 58). Bioactive printing falls under the spectrum of bioprinting, but focuses on using biocompatible plastics, such as polylactic acid, and fused deposition modeling or other 3D printing techniques to create 3D printed implants impregnated with drugs, hormones, or other agents. Weisman et al. (56) reported on 3D printed gentamicin- and methotrexate-eluting beads and constructs that showed favorable elution profiles. In an in vitro model, Tappa et al. (59) 3D printed gynecologic implants such as intrauterine devices with estrogen and progesterone incorporated into the construct’s structure. In the near future, antibiotic impregnated hardware will be custom printed to deliver therapeutic doses of medication, tailored to the individual. For patients with cancer, targeted chemotherapeutic implants will be tailored to the patient’s laboratory data, clinical evaluation and physical characteristics.

More relevant to radiologists, custom designed bioactive catheters and stents using absorbable and non-absorbable biocompatible materials are forthcoming applications of 3D printing (56, 57). Weisman et al. (57) 3D-printed a bioactive catheter modeled after a commercial drainage catheter and showed similar bacterial and tumor retarding abilities and elution profiles. Ballard et al. (58) reported a similar in vitro experiment using 3D printed antibiotic impregnated surgical hernia meshes, which inhibited bacterial growth in culture plates.

As bioactive 3D printed constructs come into clinical practice, radiologists may perform image-guided procedures using 3D printed catheters, use data from cross-sectional imaging to help customize bioactive implants prior to surgery, and interpret imaging studies in patients with personalized implants.

This technology has the potential to revolutionize healthcare far beyond making transplant waiting lists a thing of the past. Autograft printing negates immunosuppressive therapy with the associated benefit of reducing cost and morbidity In 2015, Organovo announced its first 3D printed human kidney tissue (17). Homan et al. (105) reported bioprinting of human proximal tubules and embedded them in an extracellular matrix where they were maintained for greater than two months. Similar technologies have been used to print human skin (106) and cardiac tissue (107). Printing one tissue, whether de novo or as cell progenitors onto a scaffold, is challenging. However, printing an entirely vascularized organ such as the kidney is even more difficult. Accurately replicating the architecture of blood vessels, connective tissue, and other supporting tissue in and about visceral organs are some of the biggest challenges faced by researchers. Although additive manufacturing has been used to construct organs and tissue implanted in mice and rats (101, 102), no 3D printed organ has yet been used in humans.

Laronda et al. (101) created a bioengineered 3D printed ovary and implanted them in mice with bilateral oophorectomy. The 3D printed scaffold had stiffness that mimicked ovarian tissue and a porous morphology to accommodate ovarian follicles. After populating these ovarian-like scaffolds with ovarian follicles in various stages of maturity, the 3D printed constructs demonstrated folliculogenesis and tissue growth. Some mice with the 3D printed ovarian constructs were impregnated and bore offspring. Proof-of-concept work has been done with 3D printing of porcine aortic valves as well as mechanical constructs for use in repairing bone defects (108, 109). Additional tissue engineering works includes 3D printing of a bioprinted rabbit urethra, which demonstrated promising characteristics in an in vitro model (110).

Customized 3D printed organs can be enhanced by the addition of electronic components to augment organ function. For example, Mannoor et al. (111) used 3D printing to construct a “bionic” ear, composed of living cells and electronic nanoparticles. To construct this tissue, the investigators seeded chondrocyte on an alginate hydrogel matrix as the organic component and silver nanoparticles as the conductive components. The conductive components showed good functionality with little message distortion of a classical music piece transmitted to the 3D printed bionic ears (111).

Customized devices, both biologic and synthetic, are cosmetically superior with properties matching native tissue in the case of biologic prints (112). On the larger scale, 3D bioprinting has the potential to streamline every aspect of care; from the surgeon who works alongside the radiologist to design and produce a customized bioactive mandible that is printed, sterilized and ready for implantation on demand to the interventionalist who implants a customized drug-eluting stent uniquely capable of delivering high-dose therapy to the microenvironment of interest.

Research Opportunities for Radiology—State-of-the art 3D printing relies on the optimization of imaging. Radiologists who are involved in 3D printing research can help accomplish this. They can also perform the post processing required for 3D printing, accurately and efficiently. Centralization of 3D printing, data collection and quality control in the radiology department provides many research opportunities related to 3D printing.

Current opportunities for radiology engagement include:

1. Optimization of CT and MR image acquisition is key for translating DICOM data into high-quality 3D renderings suitable for printing, and the creation of the actual models and constructs. Research in optimizing image acquisition and data

processing could include defining if CT or MR produces better anatomic models for a given disease process. With CT, this could include determine if high-resolution multiplanar reconstructions are necessary for model creation. With MR, sequences that best demonstrate a given pathology can be an area of research. MR based 3D printed models should be an active research area in addition to CT based printing, with design of new imaging sequences and techniques that can maximize the diagnostic utility of 3D models derived from MRI data (113). Additionally, additive manufacturing from 3D-acquired sonographic data may have role, particularly in prenatal ultrasound.

2. Segmentation software plays an important role in 3D printing, however it is often limited given the technology that radiology departments currently use in the clinical setting. Radiologists, in conjunction with engineering specialists should play a major role in the development of appropriate software with advanced capabilities for this purpose, as well as harness strengths of a given modality through creation of specific protocols (114). Development of such software will require FDA approval for clinical use.
3. Optimizing 3D printing workflow in the context of standard image acquisition and interpretation. 3D printing will only flourish within radiology if it can be easily integrated into a radiologist’s daily routine. Automated sectioning and transitioning to 3D printing-compatible files would be needed to optimize the workflow of a medical 3D printing lab led by radiologists.
4. There have been exciting advances in tissue engineering outside of 3D printing, such as bladders and urethras grown in laboratories and implanted in patients (115, 116). At the time of writing, 3D printed organs or tissues have not been used in humans. However, studies have demonstrated human derived tissue implanted in mice and rats in the form of ear cartilage and calvarial bone 3D printed constructs (102). Advances in 3D printing technology could potentially revolutionize organ transplantation. In nearly all areas of transplant, there are shortages of deceased donors, few living donors, and many patients on transplant waiting lists. For example, given the increasing need for liver transplantation, the relative lack of cadaveric donors, and high morbidity of healthy living donors with lobectomy, preoperative 3D-printed models can be of great benefit to patients (41, 117). Although feats such as 3D printing of human kidney tissue has been achieved (17, 105), replicating the entire architecture of a 3D printed organ is more challenging and needs to be attained before this technology is ready for use in humans.
5. Introducing training programs for residents and radiologists in the steps of 3D printing. This will create a larger pool of radiologists involved in the process, improve accuracy, and assist in the continuity and sustainability of this technology within radiology departments.
6. Demonstrating value in patient care, particularly in preoperative planning. For 3D printing to become reimbursable, further demonstration of its value will be needed. Although this has already been demonstrated in prior studies (45),

additional studies are needed. Standardizing terminology related to 3D printing. For 3D printing to become a reimbursable service provided by radiologists, it is prudent to develop a standardized lexicon on naming models, the process of printing itself, and other related factors. Chepelev et al. (118) conducted a literature search in order to standardize terminology related to 3D printing. They concluded that "3D printing", "additive manufacturing", and "rapid prototyping" are three nearly synonymous terms used to describe the concept of 3D printing. They found that by 2015, "3D printing" was the most frequent descriptor (>60%) and they advocate its use over the other two terms (118).

Challenges to Clinical Application of 3D Printing

Despite its various opportunities for improving health care, 3D printing comes with substantial challenges. This section discusses financial, regulatory, and legal obstacles to a wider clinical application of 3D printing.

Financial Challenges—Much of the popularity of 3D printing in and out of medicine is due to the fact that the technology has become more affordable. However, the capital expense of establishing a 3D service can be substantial along with time or new personnel investments to develop technical expertise. Basic requirements include software for post-processing and equipment for printing or service contracts for outsourced prints. The 3D printing service can be set up as a new lab or as an extension of an existing 3D visualization lab. A clinical 3D printing lab would require an ancillary staff to carry out the actual printing of the model, supervised by the radiologist. Justifying these costs for a healthcare system requires proof of effectiveness. Steps in the right direction are studies that show that 3D printed models help decease operative time, patient anesthesia time, and overall cost (45). The use of 3D modeling for procedural optimization may eventually demonstrate improved outcomes. For example, Wang et al. (91) created a 3D model of coronary vasculature. In vitro models were used to optimize stent placement for percutaneous intervention and determine the best stent placement based on fluid dynamics. These types of investigations will be important for demonstrating value of 3D printing.

Javan et al. (119) summarize the costs associated with producing various 3D segmented models, based on complexity. Personnel with dedicated time to perform modeling and fulfill requests need expertise and support to provide such services. Javan et al. (119) suggest that institutions with smaller budgets can reduce cost by outsourcing printing to web based services.

Quality control and accuracy of 3D printed models is another factor to consider in starting a medical 3D printing service. Leng et al. (120) advocate for a systematic approach to quality assurance of 3D printed anatomic models. The authors advocated scanning the 3D printed models with CT. The CT of the 3D printed construct is then coregistered with the reference cross sectional CT or MR. Such an approach showed great accuracy, with the error range and standard deviation of less than 1 mm. Producing high quality prints benefits from acquiring high quality images. In the case of CT, this usually means using the thinnest slice data available for reconstructions, when these multiplanar constructs are used in the creation of the stereolithography (STL) files (120).

All coding for services in the United States is coordinated by the American Medical Association using current procedural terminology (CPT) codes. Codes are used by Centers for Medicare Services to determine reimbursement levels for service. Procedures with a proven level of benefit for patients receive a level I CPT code. Unproven or experimental procedures can be granted a time-limited experimental code (e.g. CT colonoscopy).

As of 2006, there are two CPT codes for 3D modeling: 76376 - which covers models created on the acquisition scanners and 76377 – which covers models created on an independent workstation. Both CPT codes require physician supervision of the modeling process and interpretation with reporting. At this time, there are no specific CPT codes for creating customized 3D printed models from radiological data.

Through the precedent of the 3D reconstruction CPT codes, future reimbursement for 3D printing is possible. Reimbursement for a level I CPT code for 3D printing will require validation through a body of peer-reviewed literature. To date, the 3D printing literature consists mainly of case reports and small case series (45). For it to be reimbursed, 3D printing must demonstrate added value by improving patient care and/or reducing cost of delivering care.

Varied clinical applications may require complex coding that account for variables such as time to convert imaging data to 3D models and various post-processing tasks. Potential strategies for reimbursement include combining 3D printing with the diagnosis related group (DRG) charge or with the global surgery package (when 3D printing is used for operative planning).

Although technologists and radiologists can learn the technical aspects of printing constructs and models, engineers are also well suited for this task. Having radiologists involved the 3D modeling and printing process by including them in their reports will also provide a quality check mechanism that will help with validation and correct application.

Regulatory Challenges—In order to reach the general market in the United States, a medical device must meet standards set by the Food and Drug Administration (FDA). The FDA maintains classifications for approximately 1700 generic devices. Each generic type is assigned one of three classes based on standards deemed necessary to assure safety and effectiveness of a device. Di Prima et al. (121) published a narrative on the FDA's current perspective of 3D printed medical devices. The authors consider the different roles of the different regulatory centers with different roles in the approval of 3D printed products, methodologies, and materials. Additionally, they discuss the role of other regulatory agencies including the Center for Devices and Radiological Health, the Center for Drug Evaluation and Research, and the Center for Biologies Evaluation and Research. A discussion of how 3D printed constructs may be considered medical devices along with FDA definitions of types of devices follows.

Christensen and Rybicki (72) provide a narrative in which they classify anatomic models created by 3D printing, describe the quality assurance factors of each classification, and provide an opinion of how these groups might be regulated by the FDA. Groups are classified I, II, and III, which are stratified depending on the level of modification from the initial cross-sectional imaging. Group I anatomic models are models in which the organ of interest is printed from the patient's scan without any modification. In contrast, Groups II and III are models in which the patient's original anatomy has been altered. Group II is a modified anatomic model (e.g., a tumor has been digitally removed or deficit in bone is virtually filled with a graft) and Group III is a virtual surgical planning with a template in which software is used for surgical simulation. Group III may also include 3D printed constructs that are used intraoperatively. Regulation of these models is determined by whether they may be considered a 'medical device'. Group I is not considered a medical device, as no modification was performed on the patient's anatomy. Groups II and III can be considered as medical devices and may be subject to regulation by the FDA.

Class I devices are low risk and subject to general controls. An example of devices with class I designation include bandages and hand held surgical instruments. Class I devices do not present an unreasonable risk of injury or illness. Class III devices have more stringent requirements including general and special controls and must pass a premarket approval. These are usually devices that support or sustain human life. Implantable devices and diagnostic tests are examples of Class III devices (122).

Two pathways exist to allow the marketing of medical devices. The most common pathway to bring Class III devices to market is the 510(k) process which allows devices that are "substantially equivalent" to a previously marketed device to obtain clearance from the FDA as long as general and special controls are met. This pathway rarely requires clinical trials. The second pathway is the Premarket Approval (PMA) process, which is similar to pathway for new drug approval. Typically clinical trials are required for PMA (122).

The FDA has also created an alternative pathway called Humanitarian Use Device (HUD) program. This allows devices to come to market intended for patients with rare-life threatening diseases. This alternate process expedites the approval process and avoids large expense for devices that potentially benefit conditions that affect fewer than 4,000 patients in the US per year (122).

The HUD pathway is less cumbersome than the PMA pathway. It requires safety data but not effectiveness data. Morrison et al. summarize their experience in creating patient specific tracheobronchial splints using a laser sintering process under a Humanitarian Device Exemption (122).

Depending on indicated use and precedent, 3D printed medical devices will have varied requirements for approval under federal regulations. Despite rapid growth in number of 3D printable materials, the FDA has approved only a limited number of flexible, biocompatible materials. Currently, bioactive 3D printed constructs are largely experimental. Case examples in the literature reveal most 3D printed devices have been granted 510(k) or humanitarian use approval. As methodologies improve, it is not clear what level of regulation, premarket testing, and approval that these constructs will require compared to traditional implants and drugs. Bioactive 3D printing is customizable patient-specific medicine, so it may not fall under the traditional process for implant approval.

Sterilization of 3D printed implants and surgical tools is an important factor when designing constructs for procedures. Methods include printing on a sterile platform at high temperatures. Alternatively they can undergo chemical sterilization, such as glutaraldehyde. 3D printers could be housed in a sterile or substerile area, but this is not required. Although there are 3D printing techniques to print metals and other materials, resorbable and biocompatible plastics, (such as polycaprolactone and polylactic acid), are among the most frequent materials used in rapid prototyping (60, 123). Further work is also needed in standardizing sterilization techniques for constructs. Four common methods of sterilization used on medical equipment include autoclave, ethylene oxide gas, hydrogen peroxide gas plasma, and gamma radiation. The type of sterilization used will depend on the material properties. If high temperatures associated with autoclaving are not suitable, lower temperature methods are preferred but may need evaluation to confirm safety (124).

Medicolegal Challenges—There are many unanswered legal questions about 3D printing. Can physicians face litigation resulting from construction of a 3D printed model or prosthetic? The 3D printed model would need to be visually inspected to ensure no errors occurred during the printing process. Alternatively, as discussed earlier, a CT of the construct can be obtained to compare it to the reference CT or MR (120). A radiologist may need to generate a report attesting that they verified the 3D reconstruction used to generate the model and visually inspected the model itself. This would provide documentation, which would be helpful in billing and as a defense for any litigation that may arise. Cataloging anatomic models for documentation can be done through creating a physical or digital record of the model. Dual printing anatomic models is a consideration, however, this is likely impractical from a storage, resource, and time perspective. Obtaining a CT of the model could serve as a tool for both quality control with volumetric analysis and comparison to the original patient imaging and to store a surrogate for the model; however, this option would also be time and resource consuming. Likely the most practical solution is digital storage of the file used to create the 3D printed model. This could be on a dedicated storage drive or in the picture archiving and communication system in DICOM format. At the time of writing, the DICOM Standards Committee has formed a working group to facilitate conversion of the 3D files used to generate 3D printed construct into DICOM format (125). As this technology improves, such approach may facilitate easy conversion of common 3D printing files types in to DICOM format to store those images in patients' medical records.

Within the spectrum of using 3D printing for anatomic models and implantable devices, there is need for validation of regulated devices. In particular, this may apply to the Class II and III as discussed in the "Regulatory Challenges" section would require product validation, defined as metrics of quality assurance, at all stages of its production (126).

Conclusion

Radiology can be the clinical specialty to take the lead in coordinating 3D printing services: processing the imaging data, designing 3D models for preoperative planning, and working with surgeons to optimize 3D printed prostheses and bioactive implants. We must advocate for rigorous, controlled trials to assess the true utility of 3D printings many applications. In accord, radiology can provide appropriate use criteria to guide implementation of this technology into the healthcare system.

3D printed models are likely to change how we practice radiology. They can help us teach our trainees, allowing the opportunity to practice and refine technical skills in a relatively penalty free environment. This has been shown to not only augment their understanding of anatomy and pathology but translates into reduced operative times, overall savings that more than covers of the cost of the model, and improved patient outcomes (45, 127, 128). These models offer radiologists the opportunity to augment patients' relationship with and understanding of medical imaging (75, 76, 129). Radiologists may use 3D models to improve communication with referring providers as well, especially in the setting of interdisciplinary conferences. When multiple specialties are involved in patient care, 3D printed models can help illustrate complex pathology and anatomy and improve coordination of treatment. Radiologists who operate a 3D printing laboratory can add value to many different clinical service lines. There are online resources that allow the radiologist to learn about 3D printing, access previous rendered files used to print anatomic models, and collaborate with others.

The NIH 3D Print Exchange (130) is a fast growing web based platform that provides models in formats that are readily compatible with 3D printers as well as shared information to assist in creation of new models or collaborations. This repository provides a central warehouse of information that allows for national and international sharing of scientifically accurate 3D models for anatomic, educational, surgical, or research purposes. The site is interactive allowing for print uploading, sharing and engaging with other users and is an excellent resource for those interested in 3D printing. Sharing is beneficial for general models used for educational purposes to eliminate the need for segmentation and transformation of representative anatomic models. Radiologists and radiology departments may be interested in contributing to and participating in this repository.

This article reviewed various clinical applications of 3D printing that should be of interest to most radiologists. By embracing the growing field of medical 3D printing, radiologists have an opportunity to move beyond image interpretation to improve patient care.

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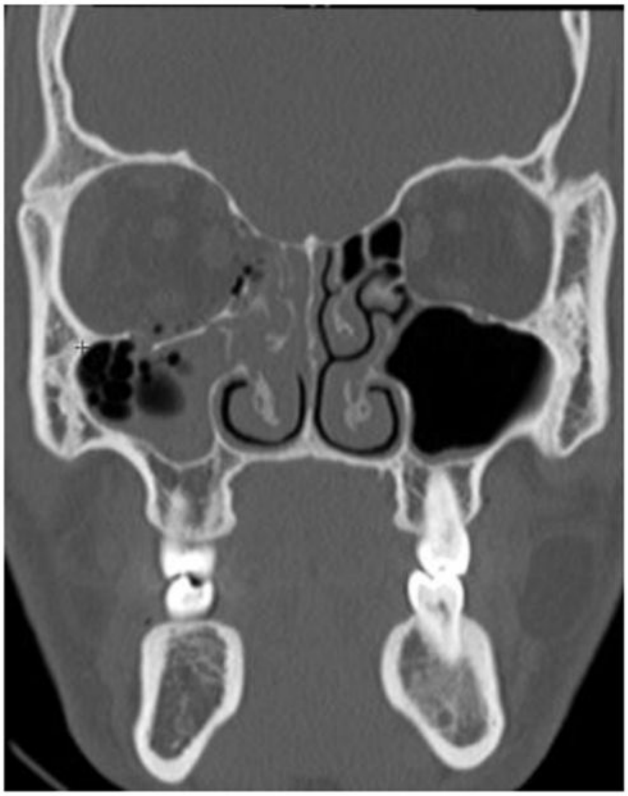

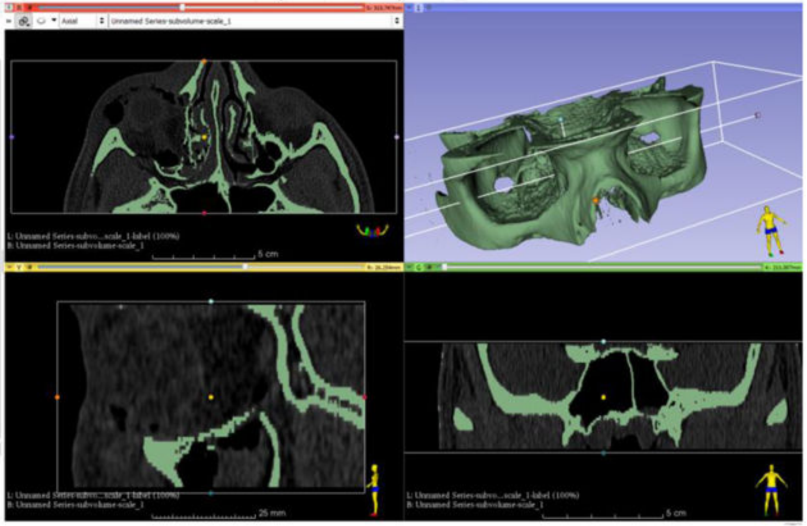
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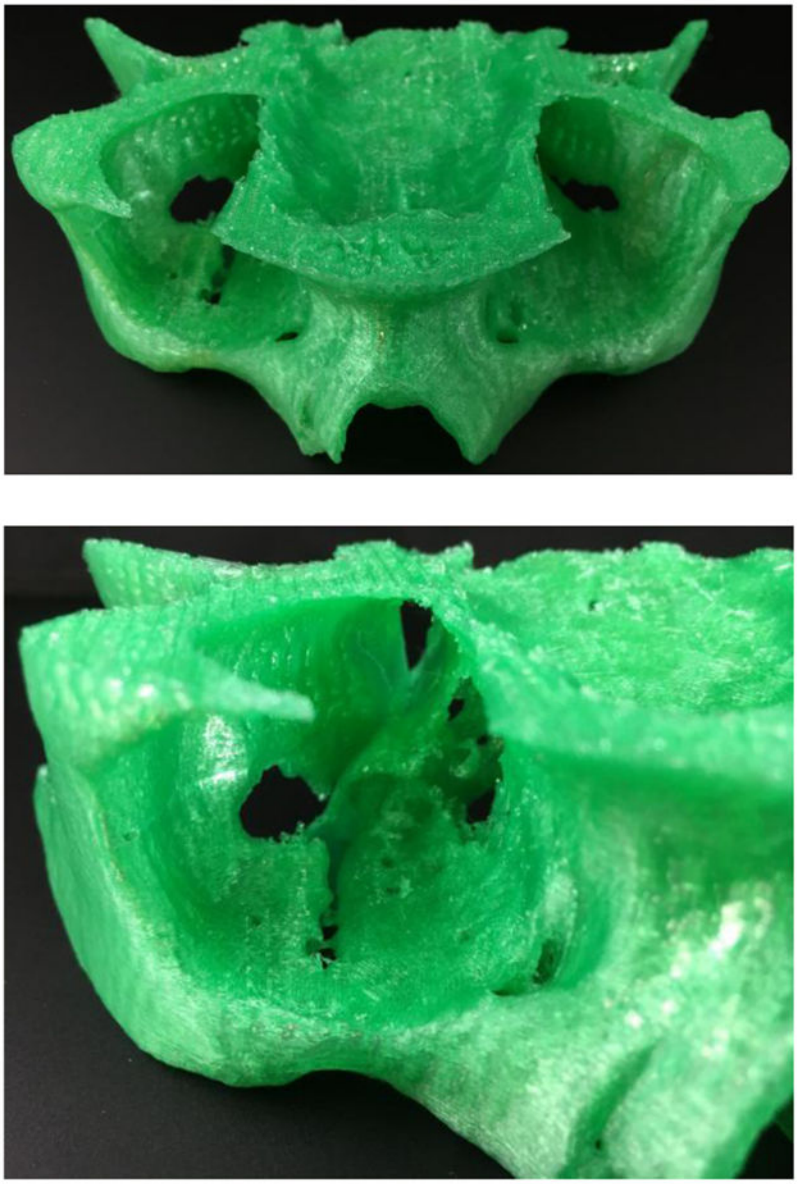

Figure 1.

3D printed model of a right orbital blowout fracture. 22-year-old man following an altercation. a. Coronal reconstructions computed tomography (CT) image of the facial bones with shows a right orbital blowout fracture involving the medial and inferior walls. b. CT DICOM data used to create a STL file (3D Slicer version 4.6, www.slicer.org). c. 3D printed anatomical model of both orbits. d. Photograph of the right orbit, which delineates the nature of the blowout fracture.


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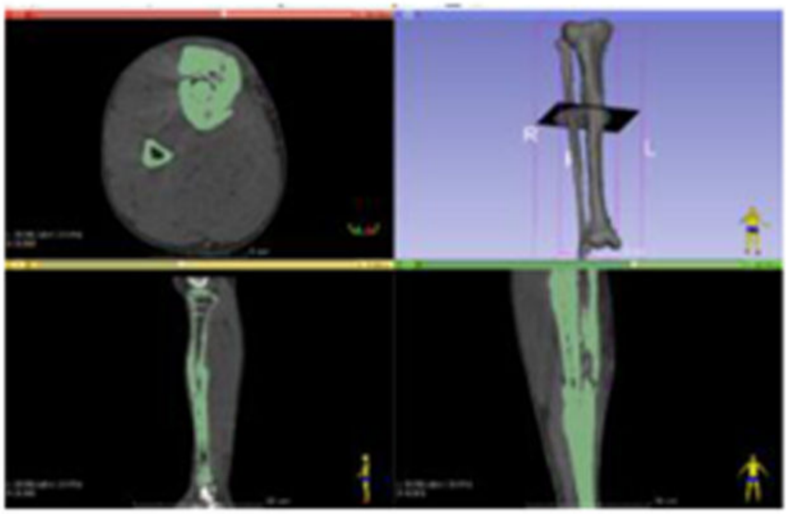
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Figure 2.

3D printed model of a tibial fracture nonunion. 42-year-old man 5 months following open reduction and internal fixation of a comminuted tibial fracture. a and b. Coronal reconstruction computed tomography (CT) image of the tibia and fibula with show a healed fibula fracture and a reduced and internally fixated, non-united tibial fracture. b. CT DICOM data used to create a STL file (3D Slicer version 4.6, www.slicer.org). Anterior (c) and posterior (d) photographs of a 3D printed anatomical model of the tibia and fibula show the orientation of the tibial fracture nonunion.

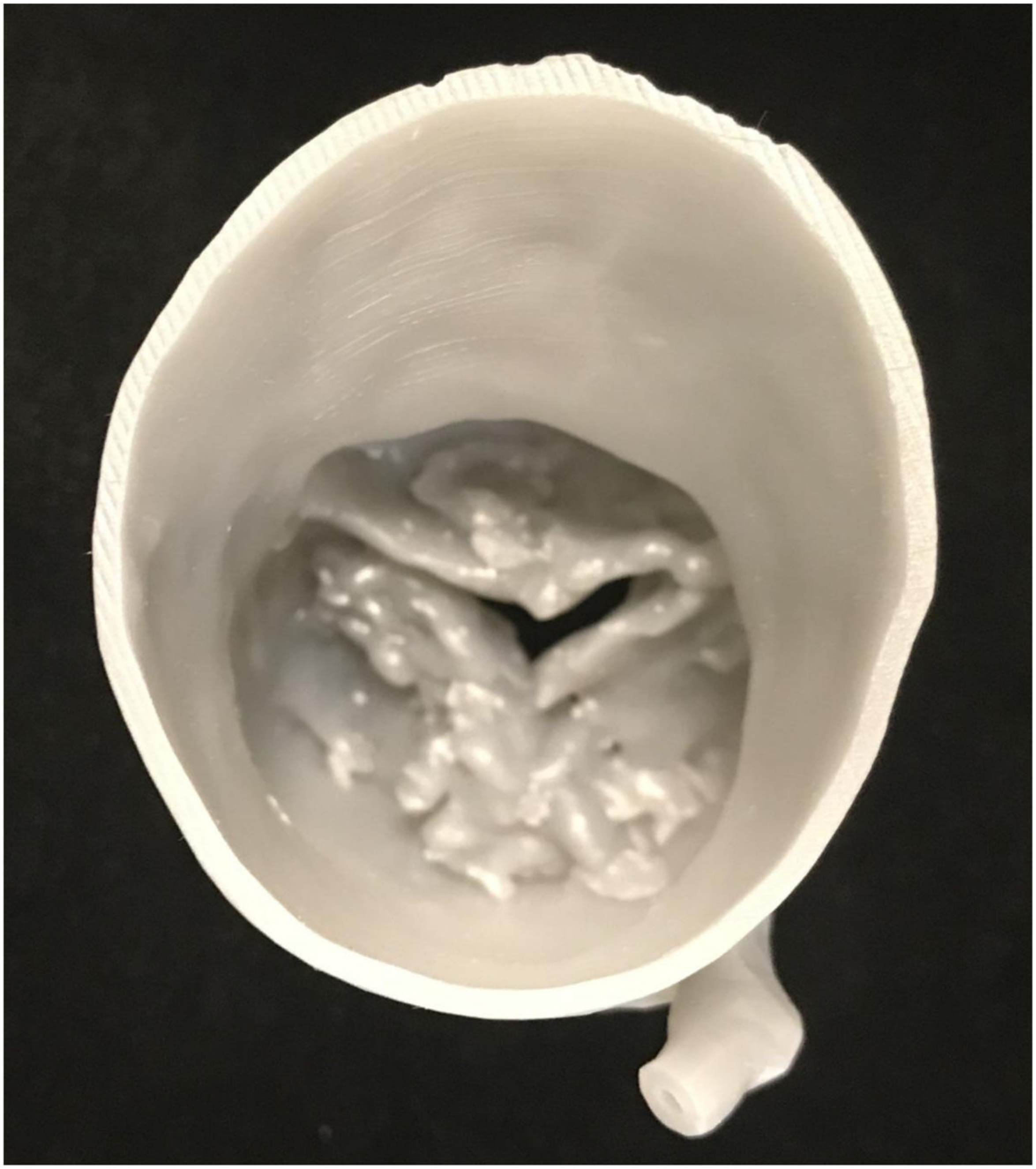

Figure 3.

Aortic root model used as a training simulation for transcatheter aortic valve replacement (TAVR). Patient specific models can be used to preoperatively size the TAVR stent. The model was fabricated using the Form 2 3D printer (Formlabs Inc, Somerville, MA) using standard resin.

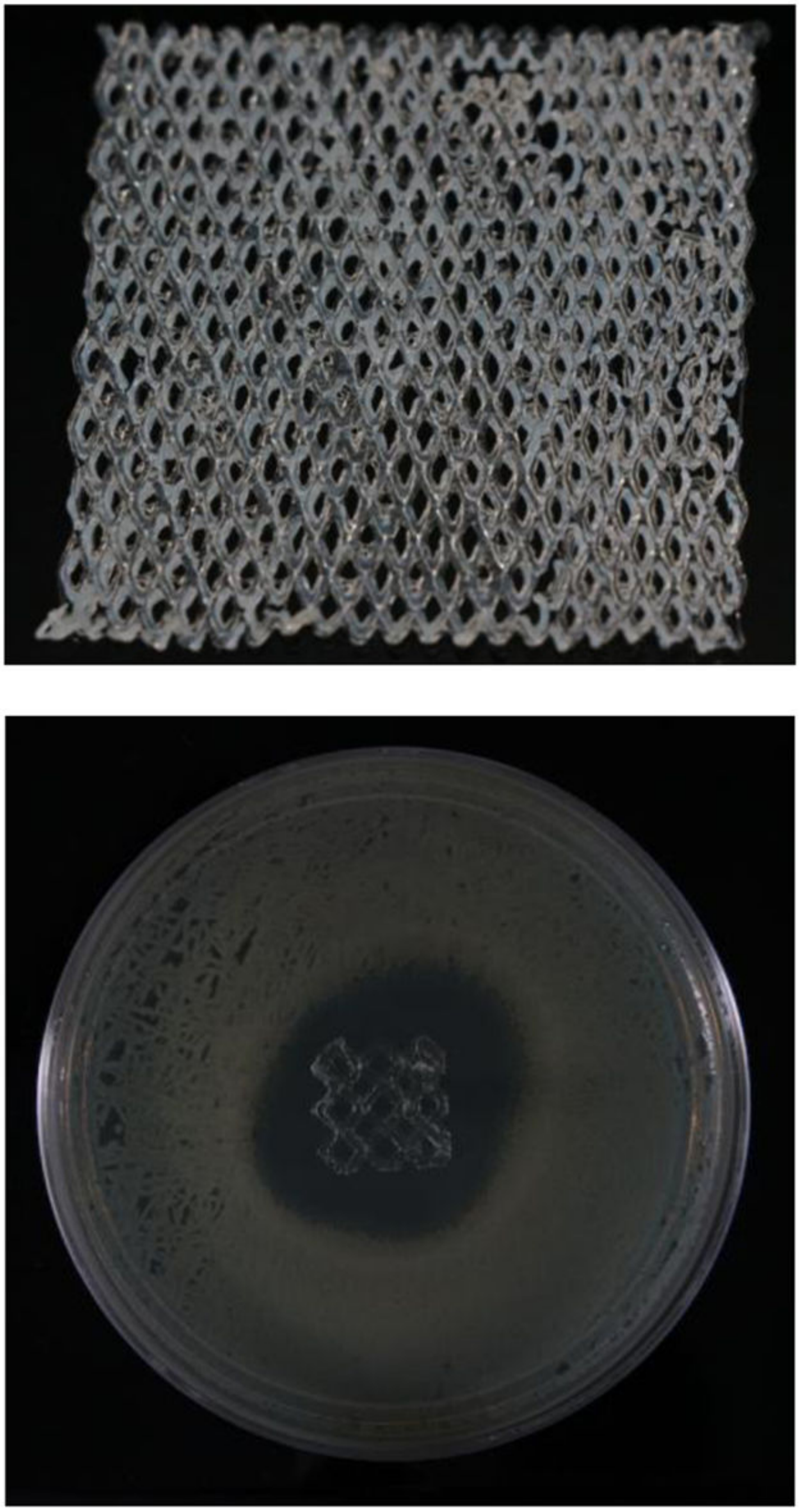

Figure 4.

3D printed drug eluting surgical meshes using fused deposition modeling. a.) Photograph of a 3D printed surgical mesh printed using both polylactic acid and polycaprolactone. These two plastics were extruded together to create the proof-of-concept mesh variable pliability.

b.) Antibiotic-eluting surgical mesh fragment shows inhibition of bacterial growth in plate culture.