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3D PRINTING OF BIOMEDICAL MATERIALS AND DEVICES

FOCUS ISSUE

Establishing a point-of-care additive manufacturing workflow for clinical use

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Additive manufacturing, or 3-Dimensional (3-D) Printing, is built with technology that utilizes layering techniques to build 3-D structures. Today, its use in medicine includes tissue and organ engineering, creation of prosthetics, the manufacturing of anatomical models for preoperative planning, education with high-fidelity simulations, and the production of surgical guides. Traditionally, these 3-D prints have been manufactured by commercial vendors. However, there are various limitations in the adaptability of these vendors to program-specific needs. Therefore, the implementation of a point-of-care in-house 3-D modeling and printing workflow that allows for customization of 3-D model production is desired. In this manuscript, we detail the process of additive manufacturing within the scope of medicine, focusing on the individual components to create a centralized in-house point-of-care manufacturing workflow. Finally, we highlight a myriad of clinical examples to demonstrate the impact that additive manufacturing brings to the field of medicine.

Introduction

Additive manufacturing, also known as 3-D printing, is built from a foundation of additive technology that utilizes layering techniques to build 3-D structures from materials such as plastic, metal, ceramics, or liquids [1, 2]. Although the original intention of 3-D printing was for rapid prototyping in the industrial and engineering fields, its usefulness was quickly adapted in the world of medicine [1]. As a first milestone, dental implants, such as clear aligners (invisible teeth straightening devices), and custom prosthetics, such as personal hearing aids, were made using 3-D printing in the 1990s & early 2000s [3, 4]. Today, its use in medicine includes tissue and organ engineering, creation of prosthetics, anatomical models for preoperative planning, education with high-fidelity simulations, and surgical guides in specialties such as orthopedics, spinal surgery, neurosurgery, cardiac surgery, and maxillofacial surgery [5, 6].

Traditionally, these 3-D models and surgical guides have been manufactured by commercial vendors, such as 3-D Systems (Rock Hill, SC, USA), Depuy Synthes (with Materialize) (West Chester, PA, USA), Onkos Surgical (orthopedic) (Parsippany, NJ, USA) Stryker (with 3-D systems) (Kalamazoo, MI, USA), and KLS Martin (Jacksonville, FL, USA) [7]. However, though effective, there are various limitations in the adaptability of these vendors to program specific needs, they normally require extended turnaround times (several weeks) for model production and accrue significant costs [8, 9]. Therefore, the implementation of a point-of-care in-house 3-D modeling and printing workflow that allows for customization to program-specific needs, rapid turnaround time for 3-D model production, and a more affordable cost may be desired at capable institutions. In addition to potential time and cost savings, creating an in-house workflow also protects HIPAA-protected patient information, as patient scans and data are no longer being sent to commercial vendors. The initial intended use of a setup aligning with this protocol is for educational and training purposes. However, following FDA guidance [10, 11], clinical applications for patient

use can be quickly extended. Point-of-care medical device manufacturing should be discussed with the FDA at some level, following applicable quality control and regulatory requirements for an in-house manufacturing center. The presented protocol hereafter is not intended for the development of an independent commercial 3-D printing/manufacturing workflow.

In this study, we detail the process of additive manufacturing within the scope of medicine, focusing not only on the techniques, materials, and printing resources essential for print production, but particularly on the digital workflow of model production, the regulatory data management guidelines that govern these processes, and the necessity of collaboration and communication among multidisciplinary teams that involve both engineers and clinicians. Furthermore, we describe the process of uniting each of these individual components of clinical additive manufacturing into a centralized in-house point-of-care manufacturing workflow. Finally, we highlight a myriad of current and future clinical examples that involve 3-D printing within the medical field to demonstrate the impact and value that additive manufacturing brings to the field of medicine.

Results: components of an 'In-House' hospital 3-D printing program

Regulatory considerations

Before implementation of a self-sufficient in-house 3-D printing program can begin, an institution must review the regulatory considerations of a 3-D printing workflow. The FDA has commented on the use of additive manufacturing models and utilizations of this technology have largely been cleared for use. The segmenting software that is used must be approved, and all devices, unless specifically exempt, must comply with the FDA's Quality System regulations; any device that follows this protocol will be in compliance with the FD&C Act [12]. Some examples of specifically exempt devices include those designed to treat unique pathologies that no other piece of equipment specifically addressed [13]. These regulations apply to devices that are manufactured both commercially or in-house, but anatomical models, specifically, are expected by the FDA to adhere to the quality system regulations to ensure that the ultimate device meets the necessary guidelines [14]. New 3-D printing projects may benefit from reading the Center for Devices and Radiological Health's Division of Industry and Consumer Education section as it provides guidance for medical device regulation. For DICOM image processing, the DICOM Standard outlines methods for keeping patient information and imaging data confidential [11]. Ultimately, the Center for Devices and Radiological Health have approved 3-D-printed models, also within software regulation standards [10, 12]. At least one medical professional organization, the Radiological Society of North America, has released guidelines for utilizing 3-D printing at the point of care, which includes recommendations on how to consistently and safely produce 3-D-printed anatomical models generated from medical imaging, as well as criteria for the clinical appropriateness of using 3-D-printed anatomical models for diagnostic use [15].

Other considerations include implantable devices and patient-specific tools. When these patient-specific implants (PSI's) are designed to replicate a unique patient's anatomy, the time from original imaging to the production and utilization of each device must be detailed as the expiration date for that device. The concern is that a patient's anatomy may change if a longer time interval elapses, thus rendering the PSI ineffective [10]. Generally, the wide-ranging devices available to additive manufacturing, such as instruments, single use and reusable devices, and standard sized devices and PSI's, all must adhere to their own respective regulatory guidelines. For example, a device that is made from a photopolymer will not need to adhere to the guidelines for powder bed fusion, and vice versa [10].

Moreover, for each printing program to be validated, it must adhere to the FDA's Technical Considerations for Additive Manufactured Medical Devices. This document outlines methods to establish proper quality control and details the variables that must be addressed when performing process validation. These methods include but are not limited to the following: beam temperature and power, build space temperature, pressure, humidity, and ultimately the end product's quality such as its dimensions, characteristics, and featured geometry. Finally, the software must also be validated according to the FDA's General Principles of Software Validation and the Code of Federal Regulations Title 21 [10].

Team

To begin this process, a multidisciplinary team consisting of both clinicians and engineers must be recruited. Here, we will begin to outline the steps and minimum necessary personnel for successful program implementation, using head and neck (H&N) tumor resection as an example. From a patient's first realized symptoms to their own 3-D model, customized reconstruction, and the post-surgical follow-up, every step requires the expertise of a myriad of specialists at an institution.

Initially, an in-house 3-D printing program for H&N cancers specifically requires a physician with interest in the various associated pathologies, and whom has the patient volume and willingness to introduce 3-D-printed materials into his or her practice. This may include otolaryngologists, neurosurgeons, or even facial plastic surgeons, among others. Once a primary physician is identified, the process begins by finding surgical candidates. Moreover, identifying patients for whom a 3-D model can be used requires a plethora of input that may benefit from a

specialized tumor board. Here, standardized decision-making methods can be realized that help ensure optimal outcomes for the patients.

A proper in-house program must have access to the CT and MRI imaging data. These data are stored as DICOM files for processing. Once adequately prepared, the most important aspect of image management remains ensuring adherence to the Health Insurance Portability and Accountability Act (HIPAA) regulations. Securing DICOM images within the primary institution's firewall isn't difficult, but the challenge arises when trying to send confidential DICOM images to an off-campus site for manipulation. For DICOM images specifically, there are over 4500 fields that can be present in the "header" title of the image that may be in consideration to help keep the file confidential [11].

The DICOM Standard outlines methods for protecting patient information, and extensively details how to de-identify images and data with the "Basic Application-Level Confidentiality Profile", highlighting about 10 mechanisms to help keep patient information de-identified. Another method for encryption is "Full encryption" defined in the "Basic DICOM Media Security Profile" within the DICOM standards [16]. This method utilizes Cryptographic Message Syntax (CMS) and is an adequate approach for ensuring encryption across databases. Finally, important aspects for security are included within the PACS (Picture Archiving and Communication Systems) network and can be secured within an institution's firewall, as well as with user specific access, and detection systems that uncover breaches in network security [17]. Adequate measures can always be checked against the DICOM standards and must be given emphasis as a breach in confidentiality could be catastrophic.

Utilizing the DICOM files, an engineering team can reconstruct the 3-D-printed parts and run the printers to manufacture the patient-specific model. Once the printing process is complete and the model is delivered to the clinical destination, it may be sterilized within proper quality and control regulation guidelines and delivered to the appropriate location per hospital guidelines. Adequate sterilization may require case-by-case individualized assessment and is contingent on the materials used in the printer, instructions for use from the material manufacturers and requirements of the hospital [18].

With each printed model there is extensive feedback between the engineers and the clinicians involved that improves the subsequent models. For example, if a H&N mandibular resection segmentation process distorts the true patient anatomy in a way that interferes with intraoperative use, then the clinician can report this information to the multidisciplinary team and the necessary adjustments can be made. A detailed summary of this process is depicted as a flowchart in Fig. 1.

Given the ongoing technological advancements involving 3-D printing, including novel 3-D printing techniques, materials, printers, and applications, the presented framework, and personnel within it must be equipped to safely adopt emerging practices and protocols. Many of these future advancements are addressed later in this paper and are exciting possible extensions to this framework. Once a team, workflow, regulatory expertise and quality control system are established, incorporation of new technology and integration of new techniques can more seamlessly be integrated. As each advancement is fully realized, the multidisciplinary team must continue to practice effective feedback to consistently ensure optimal model creation.

Some components of this framework are more easily attainable and implementable than others. For example, the regulatory guidelines for proper medical use have been previously established by the FDA and are easily accessible, the clinical printers and materials are widely available, and the clinical applications have been extensively researched and utilized. However, the more difficult aspects of setting up the proposed in-house model is finding an institution that has ample clinical volume, funding, and resources (both physical space and human resources) necessary to support it. A prospective institution must realize and amend all the necessary components prior to initiating the beginning of this framework to ensure that it truly can financially and physically back a 3-D printing program.

Reimbursements

CPT (current procedural terminology) codes are used in the United States (U.S.) by Centers for Medicare Services to estimate the reimbursement amounts for certain medical services. A level I CPT code classifies a procedure that maintains a proven benefit in the management of patients and offers reimbursements to the medical institution that provides such a procedure. There have been 3-D modeling CPT codes released in the USA; however, these codes lack validation through peer-reviewed studies and randomized-control trials and thus are not yet classified as a level I CPT code [5]. As more institutions adopt 3-D printing and integrate it into their delivery of medical and surgical care to patients, more data will emerge, and more powerful studies will be conducted that ultimately lead to the reimbursement of medical services involving 3-D models. Various revenue stream models can be designed for in-house 3-D printing workflows to cover material and labor costs but are dependent on the end-use and deliverables as well as the institutional norms.

Challenges

3-D printing can be used in the development of medical devices, surgical optimization, bioprinting, tissue engineering, and many more applications in medicine and biomedical research. However, one of the main challenges in setting up an in-house 3-D printing program is finding adequate funding. Thus, grant

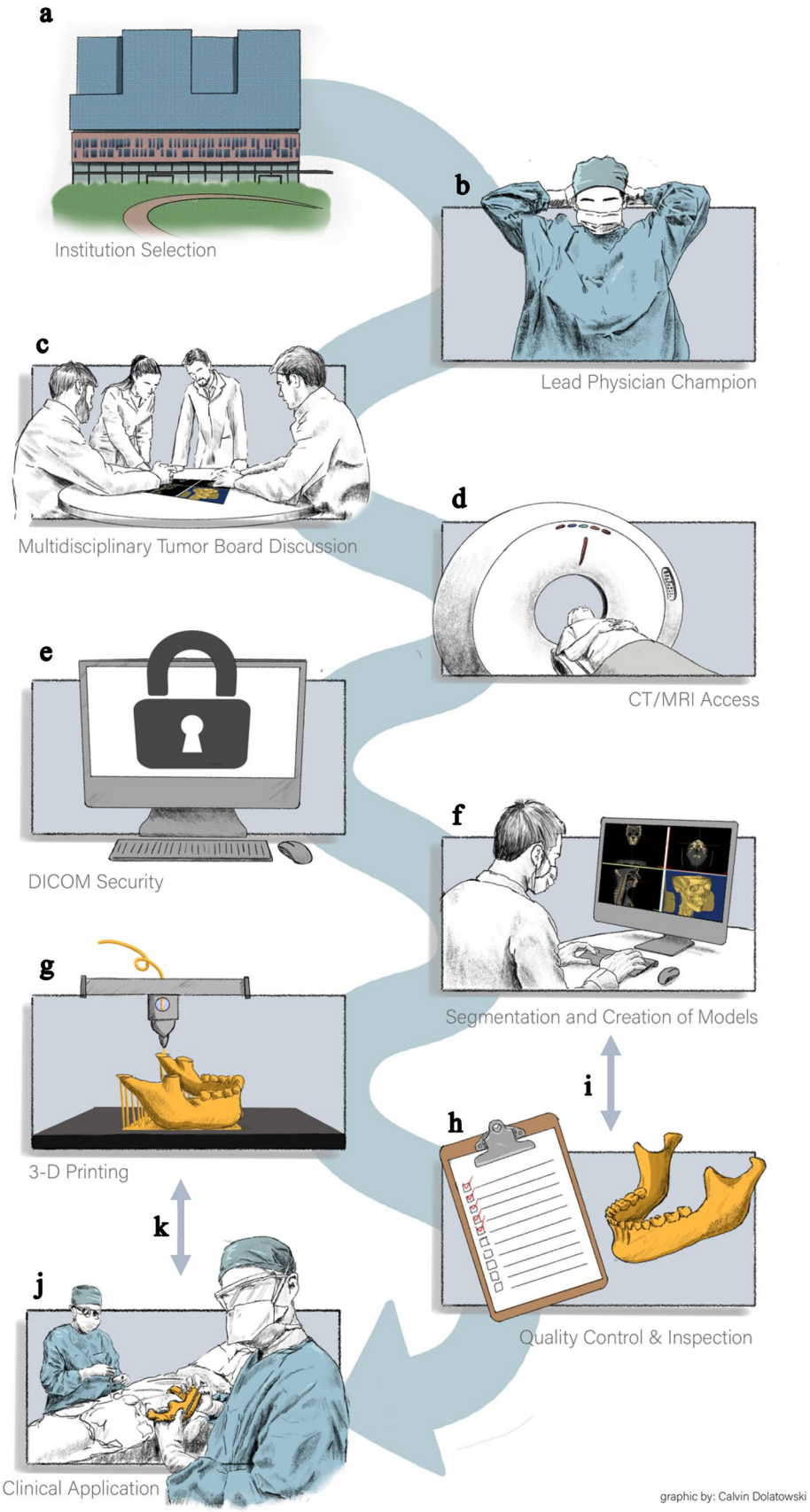

Figure 1: (a) Identify an institution that has the case volume and proper imaging equipment to support a self-sufficient 3-D printing lab; (b) Recruit a lead physician (surgeon, radiologist, etc.) to champion 3-D printing efforts; (c) Utilize tumor board, trauma cases, and other clinical scenarios that identify a wide range of patients who could benefit from 3-D models; (d) Ensure proper cross-sectional imaging (CT/MRI) Digital Imaging and Communications in Medicine (DICOM) access; (e) Ensure DICOM storage for selected patients remaining under the institution's HIPAA-protected firewall; (f) Engineering team manipulates each patient's specific imaging and creates 3-D Computer-Aided Design (CAD); (g) Final CAD model print execution per clinical requirements; (h) Quality control for proper sterilization and model preparation for clinical use in the operating room; (i) Feedback loop between Quality Control & Inspection and Segmentation and Creation of Models to improve future prints; (j) Deliver the model for clinical application per institutional requirements; and (k) Feedback loop between Clinical Application and 3-D Printing to improve future prints.

funding remains an important method of funding both research in 3-D printing and the integration of 3-D printing into hospital systems. The National Institute of Health (NIH) is the main supporter of biomedical research funding; however, there are many of government agencies as well as private organizations that provide funding. For institutions that desire to begin incorporating 3-D printing into various medical and surgical services, the names of a variety of current grants are listed here: Strengthening Career and Technical Education for the 21st Century – Carl D. Perkins V Formula Grants (U.S. Department of Education pass-through to State Education Agencies); Advanced Technological Education (National Science Foundation); Apprenticeships: Closing the Skills Gap (U.S. Department of Labor); Navy & Marine Corps STEM Education & Workforce Program (Department of Defense, Office of Naval Research) [19]. Another challenge includes the recruitment of and effective communication with multidisciplinary teams. Recruiting and communicating with a multidisciplinary team takes time and effort to foster the growth of an accepting environment, open to opinions from clinicians, engineers, and students alike. This can be difficult as clinicians, engineers, and students may all have different problem-solving methods, communication styles, and skill sets that must be carefully blended for optimal workflow. Setting clear goals and expectations at the onset of collaboration is of primordial importance to achieve success. Still other challenges that exist include competition from commercial vendors, quality control and regulation, and acquiring proper lab space and materials; all are addressed in earlier sections of this paper. The establishment of an in-house clinical workflow sets the stage for continually evolving research and development at an institution.

Methods

Printing resources

There are many available techniques in 3-D printing, each of which involve the utilization of unique materials [20]. The most used processes in medicine and their commonly associated materials will be hereafter highlighted and include the following: extrusion-based printing, powder-based printing, vat-polymerization-based printing, and droplet-based printing [21–24]. An abbreviated table describing each of the major 3-D printing techniques and their associated materials, biomedical applications, and specific printer brand correlates can be found in Table 1.

Extrusion-based printing, better known as fused deposition modeling (FDM)/fused filament fabrication (FFF), is a technique based around the extrusion of a composite, thermoplastic, or biomaterial substance through one or multiple heated extrusion head nozzles [28–30]. The materials are then layered on top of one another in vertical and horizontal directions based on the movement of the nozzle heads [31]. This technique has evolved into precision extrusion deposition (PED), precise extrusion manufacturing (PEM), and multiple heads deposition extrusion (MDHS) that are now employed for the bioprinting of lower resolution boney, vascular, and soft tissue models [32–34]. Some of the most common materials used in FDM are acrylonitrile butadiene styrene (ABS), polylactic acid (PLA), nylon, polycarbonate, polyvinyl alcohol, and polycaprolactone (PCL) [30, 35]. Both PLA and PCL are biocompatible and biodegradable and can be used in drug or implanted device creation, whereas ABS is used to create surgical models that help with education, planning, and simulations [36]. Bioprintable materials used in extrusion-based printing include collagen, gelatin, hyaluronic acid, alginate, and polyethylene glycol and are often used to generate scaffolding that allows for the regeneration of a variety of human tissues [37]. Commonly utilized desktop 3-D printer models for FDM include Ultimaker (Ultimaker, Geldermalsen Netherlands) and Protos (RepRap, Feldkirchen, Germany) among many others commercial grade options [38].

Powder-based 3-D printing can be further broken down into four subcategories, which include selective laser sintering (SLS), selective laser melting (SLM), direct metal laser sintering (DMLS), and electron beam melting (EBM) [21, 39, 40]. Each of these are rooted in generating melted or connected powder by localized heating that is then used to construct the desired 3-D product. SLS and DMLS bind the powder particles based on the pattern traced by a laser, while SLM and EBM fully melt the powder with the laser and electron beam, respectively. This invariably leads to lost details in the microstructures of printed models as compared to sintering, but SLM/EBM printed models have superior mechanical, tribological, and corrosion properties [41]. Many of the materials SLS printers utilize include either nylon or titanium powders, but can also incorporate aluminum, iron, copper, and cobalt based [41]. EBM printers mainly involve the use of cobalt-chrome alloy, and titanium materials [20].

The vat-polymerization-based printing technique employs a resin material cured in light that directs hardening of the polymerization process [42]. More specifically, a beam of laser or light is shown onto a vat of photosensitive polymer resin and the polymer is subsequently polymerized in a spatially localized pattern [43]. The most frequently used sub-types of this printing are digital light processing (DLP), stereolithography (SLA), and multiphoton polymerization (MPP). In fact, in 1994, SLA was the first technique in 3-D printing to be utilized in the medical field [44]. Mechanistically, SLA uses a spot laser to irradiate the resin in a single x–y direction, while DLP irradiates the entire plane of the x–y field while the platform with resin moves vertically in the z plane. MPP, in contrast, is irradiated in multiple directions within and outside of the x–y plane. The 3-D models printed using these various types of vat-polymerization necessitate exposure to light after the process of printing is complete to

TABLE 1: The various 3-D printing techniques and a description of each process is detailed.

Various characteristics of 3-D printing				
Printing technique	Process description	Materials	Biomedical applications	Printer examples
Extrusion-Based Printing: (1) [1]FDM; (2) Bioprinting	(1) Object is created through the layering of a melted thermoplastic material; (2) A nozzle is used to lay down biologic materials until scaffold is built [25]	(1) ABS[2], PLA[3], nylon; (2) Alginate, gelatin, collagen, fibrin	(1) Produces anatomical models (both rigid and soft) for surgical planning and preparation; (2) Used in the bioprinting of tissues, organs and cell culture scaffolds	(1) *Ultimaker 2 (UM2), Protos v3 (PR3), GAURORA 3-d Desktop FDM Printer, PowerSpec 3-D Pro; (2)* 3-D Bioprinting Solutions' FABIOB
Material Sintering (Powder-Based Printing): (1) [4]SLS; (2) [5]EBM	(1) Powdered materials are fused together by a high-power laser beam in a layer-by-layer pattern [26]; (2) Same as SLS, except an electron beam is used	(1) Nylon, polyamide; (2) cobalt-chrome alloy, titanium	(1 & 2) Craniofacial and orthopedic metallic implants, temporary rigid implants	*(1) 3-D Systems ProJet 1200, DWS Lab Xfab (2) Arcam Q20*
Material Sintering (Vat Polymerization-Based Printing): (1) [6]SLA; (2) [7]CLIP	(1) Photo-polymer resin is selectively hardened in layers using a UV laser beam; (2) Same as SLA, except UV beam travels from bottom of resin through transparent window and build platform raises object [26]	(1 &2) Photopolymers	(1 & 2) Used for printing of both soft and hard tissues for surgical planning, microneedle production	(1) Form 3 *SLA 3-D Printer, NextDent 5100; (2)* Carbon Digital Light Synthesis™
Droplet-Based Printing: (1) Binder Jetting/Inkjet; (2) Polyjet	(1) Liquid-based binding material layered onto powder bed in an alternating fashion until object is completely formed [27]; (2) Same as inkjet, except a photopolymer resin is layered instead of a binding agent, and this liquid polymer is then cured with UV light	(1) Starch & gypsum serve as powder beds, water, phosphoric acid, citric acid, [8]PDLLA function as binding agent; (2) polystyrene, polycarbonate, polypropylene	(1 & 2) Various scaffolds dedicated to cell culturing as well as soft tissue and organ development[47]	(1) *Addwii X1, ExOne R2, ZCorp Spectrum z510;* (2) Connex3 Objet500 (gold standard for 3-D model printing for surgical models), *ABS 3-D printer, PLA 3-D printer, HP Multi Jet Fusion*

Furthermore, the most used materials and biomedical applications for each technique are indicated. Finally, a non-comprehensive list of example 3-D printers on the market are correlated with each 3-D printing technique.

[1]FDM: Fusion Deposition Modeling; [2]ABS: acrylonitrile butadiene styrene; [3]PLA: polylactic acid; [4]SLS: Selective Laser Sintering; [5]EBM: Electron Beam Manufacturing; [6]SLA: Stereolithography; [7]Continuous Liquid Interface Production; [8]PDLLA: poly-DL-lactide.

ensure stability of the product [45]. Polyacrylate or epoxy resins are the most popularly used materials with SLA printers. However, for biomedically specific applications, polymer ceramic composite resins constructed from calcium phosphate salts are commonly employed [46]. Furthermore, NextDent (Nextdent B.V., Soesterberg, Netherlands) and FormLabs (Form2, Formlabs Inc., Somerville, MA, USA) companies have SLA desktop printers with various biocompatible resins [47].

Finally, droplet-based printing, or material jetting technology, involves the ejection of droplets of liquid materials through a series of jets, which polymerizes the droplets in a pattern guided by ultraviolet (UV) light [48]. Material jetting technology consists of binder jet printing (BJP), aerosol jet printing (AJP), and poly jet printing (PJP) [49]. Each of these differ in the materials used (i.e., metals, polymers, ceramics), temperature of printing, and each are suitable for the printing of certain structures (refined products, biomanufacturing products, etc.) [50, 51]. BJP commonly involves the use of water, citric acid, poly-DL-lactide (PDLLA), polyvinyl alcohol (PVA) and phosphoric acid as binding materials. Powdered materials used in BJP include composites such as hydroxyapatite, β-tricalcium phosphate powders as well as various photopolymers. An example of a commercially available 3-D PJP printer is Objet 30 PrimeTM (Stratasys Ltd., Minneapolis, MN, USA), which employs photopolymer resins such as MED610 (Stratasys Ltd., Minneapolis, MN, USA) [47].

Modeling and segmentation software

Being familiar with the process of operating various software programs is inseparable from 3-D printing, as the very ability to print a 3-D object is based on a digital representation created with such software [52]. The process of creating a digital 3-D model varies slightly between various programs, but the general process will be briefly described: (1) Data Acquisition: patient-specific models and devices hinge on first obtaining a high-resolution digital representation of the patient's anatomy. Typically, this is done via cross-sectional imaging such as Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). CT utilizes traditional X-ray technology to provide detailed visualization of the bony anatomy and limited soft tissue resolution. However, MRI utilizes a powerful magnetic field and pulsed radio waves to provide better soft tissue delineation with more limited resolution in the bony anatomy; each unique region of interest of a patient's anatomy determines which imaging modality to utilize. With both CT and MRI, the anatomic data are then stored as DICOM (Digital Imaging and Communications in Medicine) images as a series of 'stacked' 2-D pictures of the cross-sectional anatomy. (2) Segmentation: this process involves isolating or highlighting the pixels of interest from each of the cross-sectional images to build a 3-D model of only the pertinent anatomy. This may be the bony anatomy such as the mandible, the geometry of a particular vascular region, or a tumor's orientation relative to critical structures. Using a medical segmentation software (see below), these regions of interest can then be extrapolated into a full 3-D model based on the pixel size and slice thickness, both of which are embedded in the DICOM files [53]. (3) Geometric: after building the initial 3-D model through segmenting of the DICOM data, it is often necessary to digitally 'clean' the model to match the anatomy more precisely. Any excessive pixilation from low-resolution scans can be smoothed, artifact such as dental amalgam or motion can be accounted for, and areas that lacked clarity on the original DICOM can be further resolved with a basic understanding of the anatomy of interest. The model must also be optimized for printing by eliminating enclosed cavities or overly thin features as able, and a patient label may be added. (4) The model is then printed using a 3-D printer [52, 54, 55, 56]. A summary of this process using a 3-D-printed mandible as an example is detailed in Fig. 2.

Once printed, the model undergoes post-processing, which requires cleaning and refining the raw printed product for final presentation/delivery. As an example, SLA printers require a post-print wash to remove uncured resin, followed by an ultraviolet cure process to achieve final desired material properties. Supports must often be removed and touch points polished for a final deliverable product. Specific post-processing details such as the percent of isopropyl alcohol used for washing, curing temperature, and the time length of both processes varies based on the individual manufacturer, the type of 3-D printer, and the particular material being used [57]. Powder-based printers similarly require a post-processing workflow including removal of the unsintered powder and polishing of the final product. Once completed, the surgical models can ben autoclaved per manufacturers guidelines and ready for sterile intraoperative use.

In general, there is a wide variety of software options: less expensive software for research purposes as well as more expensive software that adhere to FDA (Food & Drug Administration) guidelines if utilization in the hospital setting is desired. For example, Osirix can be employed for research and development purposes, while Materialize Mimics is better suited for clinical use [7, 58, 59]. For further information regarding modeling and segmentation software, Catherine et al.provides a comprehensive overview of both research directed and more clinically geared options [60].

Associated costs

The cost of 3-D printing systems has decreased dramatically since many are now off-patent, which has opened up opportunity for integration and use within the medical field [61]. First, it is important to decide if the 3-D printing should be

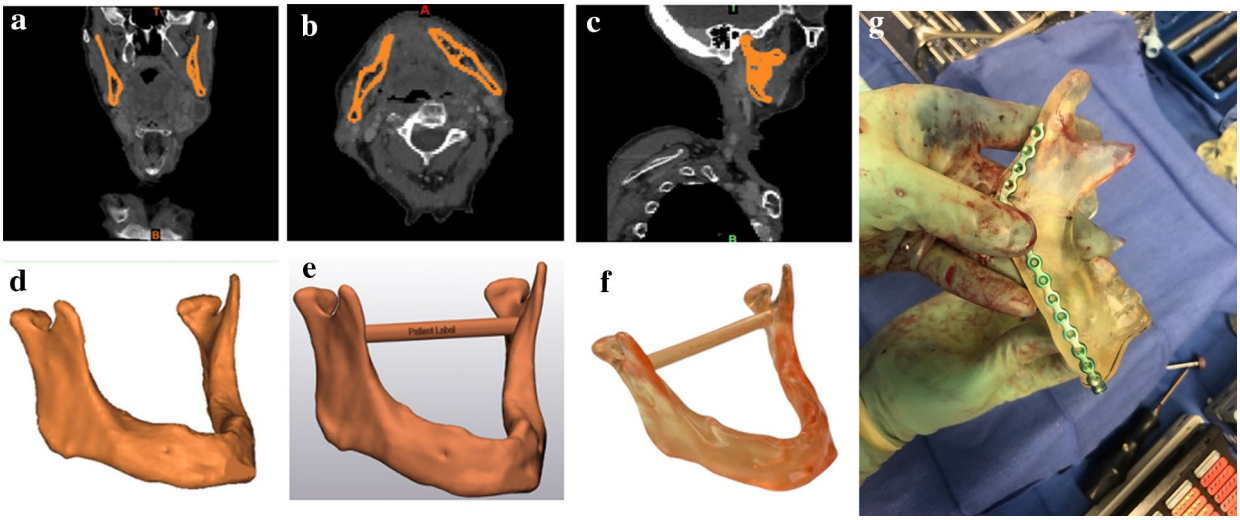

Figure 2: (a–c) Computed Tomography (CT) scan imported and isolated using Materialize 3-matic; (d) Cropped 3-D mandible model in Materialize 3-matic; (e) Final mandible in PreForm prior to printing; (f) Printed final mandible with post-processing complete; (g) Autoclaved sterilized mandible model being used intraoperatively for reconstructive surgery.

done in-house or commercially sourced, and there are indications for each. For example, the use of a commercial service over an in-house printing program may be justified in a situation of low output printing. However, in high-volume printing situations, investment in a home-grown printing system, while initially high, will eventually lead to a low-cost production of each unit [52]. A typical cost for entry-level SLA, FDM, and PolyJet systems is estimated to be $2,000–5,000, while the most sophisticated and highly accurate systems can range from $150,000-$900,000 [56]. The cost of software for pre-modeling and segmentation can range from free in price to $500-$20,000 or more depending on the type of software purchased and its intended applications. For example, beginner software is less expensive, while more state-of-the-art software that adheres to regulatory guidelines and is approved for clinical use is more expensive [52, 54].

The cost of materials used in 3-D printing is also highly variable as depending on the type and quality that is purchased. For example, polylactic acid (PLA) surgical retractors based out of the navy/army were reported to cost $0.46, while a stainless steel bone reduction clamp was reported to be $1,200 [54]. For a maximal return on investment, it is critical for institutions to properly evaluate their financial situations and goals for 3-D printing and orchestrate the integration of 3-D printing with these variables held in mind. A further categorization of the cost of various types of 3-D printers, materials, and software is illustrated in Table 2.

Current applications in medicine

Education and surgical simulation

As an educative tool, 3-D printing has been widely utilized to augment patient, trainee, and physician education. For example, a previous study compared the effectiveness of 3-D-printed models to viewing 3-D rendered images with respect to preoperative planning in pancreatic cancer. Residents who were able to review the 3-D-printed models scored significantly higher and thus formulated more robust surgical plans than those who were

TABLE 2: The most common 3-D printing techniques with cost ranges of their associated printers, materials, and software are detailed.

3-D Printing Techniques						
	[1]FDM	Bioprinting	[2]EBM	[3]SLS	[4]SLA	[5]PJP
Associated Costs						
Printer Cost Range	$200-$6,000	$10,000-$200,000	$100,000-$1,000,000	$5,000-$200,000	$3,500-$80,000	$20,000-$100,000
Materials Cost Range	$15-$600 per kg	$40-$1,000 per 20 mL	$80-$600 per kg	$45-$100 per kg	$40-$500 per liter	$100-$1000 per liter
[6]Software & Their Costs	Meshmixer *(Free)*, Blender *(Free)*, Osirex *(Free)*, Ultimaker Cura *(Free)*, Autodesk Product Design and Manufacturing *($325 per year)*, Fusion 360 *($495 per year)*, Onshape *($1,500 per year)*, Materialize Magics *(up to $20,000 initial purchase with variable rates thereafter)*					

[1]FDM: Fusion Deposition Modeling; [2]EBM: Electron Beam Manufacturing; [3]SLS: Selective Laser Sintering; [4]SLA: Stereolithography; [5]PolyJet Printing; [6]Compatibility between software and 3-D printer can vary.

only able to view the images. The authors attributed this finding most significantly to a difference in knowledge pertaining to the most important surgical steps, demonstrating the importance of appreciating the fine details for surgical approaches only elucidated through a 3-D-printed model [62]. Furthermore, 3-D simulators can be utilized in place of cadaver training, which allows for more patient-specific treatment planning and mitigates the challenges that arise from both the cost and availability of cadavers while still presenting high-fidelity anatomic realism for the learner [6]. These surgical simulators offer an excellent opportunity to augment surgical education for undergraduate and medical students, residents, fellows, and even the patient to improve education [5, 63, 64].

Moreover, 3-D printing has recently begun to include haptic feedback mechanisms into its modeling to further aid in mapping true anatomical nuances and help with preoperative planning and better operative simulations. This requires utilization of various material properties in the 3-D-printed constructs to better simulate different bony and soft tissue anatomy. One such model was developed for orbital surgery where a device was constructed to simulate the sensation of both the soft and hard tissue surrounding the anatomy of interest. Within both the oral and maxillofacial surgical trainee group and the consultant group, both subjectively were able to better appreciate the relevant anatomy [65]. These education models can be especially useful when trying to train young clinicians in uncommon and dangerous clinical scenarios. For example, an internal carotid artery injury is a rare and disastrous complication of endoscopic endonasal surgery that can easily lead to patient demise if not adequately managed, thus training opportunities for inexperienced trainees are scarce. Maza et al.assessed the use of a laser-sintered surgical simulation model to help educate and train these clinicians and found that with practice, there was a reduction in time to hemostasis, reduction in blood loss, and the training improved the confidence in over 95% of participants; these findings proved the effectiveness of utilizing a realistic model [66].

H&N tumor resections, among other surgeries, requires extensive expertise and experience before the surgeon may feel comfortable with the possible complications; however, trainees rarely have enough opportunities to hone their competence in the operating room. A long lasting, readily reproducible, and ever improving option remains the adoption of 3-D-printed physical simulators. Realistically mimicking complex anatomy that includes correct tactile feedback remains a challenge, but with an ever-evolving industry, is becoming more and more possible. Many simulations must rely on qualitative data, with various studies employing a 5-Point Likert scale and the subjective feedback of experienced surgeons; nonetheless, the response is promising [67–70]. In one neurosurgery simulation, the authors were able to mimic the brain stem, lobes, cerebral arteries and vascular walls of the Circle of Willis, crafting example aneurysms in common locations. Utilizing 3-D printing, they limited the error of true vascular wall thickness by 2–5%, and were within about 5% of matching the true characteristics of the surrounding blood vessels [71]. This positive feedback was echoed in another study examining neurosurgical aneurysm clipping simulation; the majority of participants (84%) noted that training with the use of a 3-D model was a better alternative than the traditional training methods [69]. Taking advantage of realistic 3-D models is not limited to neurosurgery and is becoming more extensively exploited in other fields. For example, in cardiothoracic surgery, 3-D-printed mitral valve models that characterize the nature of the tissue's response while suturing was similar to the realism, tensile strength, and anatomic appearance of the models [70]. Still other models printed that helped training for laparoscopic cholecystectomies found that out of the thirteen surgeons assessed on the 5-point Likert scale, the average response was a 4.5/5 in agreement that the training had realistic anatomical appearances and recommended its use in future surgical training [67].

In Otolaryngology, temporal bone modeling for simulated surgeries have been widely accepted and have helped train residents and fellows with realistic tactile feedback, specifically while drilling. Effort was placed into developing a low-cost simulation model, and is now widely utilized for education, among other dissection models for both adult and pediatric populations [72–74]. Applications remain in outlining difficult airways for unique intubation approaches for challenging oropharyngeal, laryngeal, and hypopharyngeal tumors [75], nasal and paranasal sinus pathology [76], and still others are utilizing preoperative simulations to assists in other orthognathic surgery [77]. Printing for temporomandibular joint reconstruction with customized accurate anatomical spacers that allowed for impregnation with antibiotics, is just another way 3-D-printed models are further advancing the field [78]. Ongoing research remains in otolaryngology with prospective studies examining the use of surgical simulation kits [79]. Still, further uses remain in orbital surgery practice and anatomical teaching [80], plastic surgery cleft lip and palate models [81] and in orthopedic surgery [82], among many others. As these models continue to improve, 3-D simulation may become the mainstay for better patient and anatomy specific preoperative rehearsal, and ultimately, may help improve overall surgical outcomes.

Custom fit surgical approaches & complex anatomic representation

One of the most widely used applications of 3-D printing is the ability to create patient-specific approaches that ensure optimal surgical approaches and help to minimize complications related to poorly visualized or complex anatomy. Currently, standard

imaging with MRI, CT, and ultrasound typically allows for adequate initial visualization of a tumor and the surrounding anatomy. Nevertheless, the conventional two-dimensional visualization of these technologies may lack an exhaustive representation of the complex anatomy in certain situations. Clinicians are accustomed to scrolling through a series of 2-dimensional 'stacked' images of a patient's cross-sectional imaging and mentally re-creating the 3-dimensional anatomy. However, in complex anatomic situation, a 3-dimensional model of the anatomy of interest may provide significantly more insight into the clinical picture and allow a more complete treatment plan to be devised. One such example is the use of fetal MRI to help develop a delivery strategy for a fetus with potential airway obstruction. Ultrasound suggested a facial mass that appeared to be obstructing the airway but was limited in visualization. A fetal MRI failed to demonstrate the anatomy in conventional 2-D imaging, but a 3-D-printed reconstruction of the isolated fetus allowed the team to visualize the airway and facial anatomy, making a safe delivery plan; this process is detailed in Fig. 3 [83].

In cancer operations, in which large segments of tissue are being removed, 3-D modeling and printing can be utilized to better exemplify the consequent deformity (after a 'digital' resection) and allow for a more personalized reconstruction plan to meet each patient's anatomy [84]. Moreover, 3-D models can better represent pertinent anatomy, better simulate the planned surgery, and more adequately depict intraoperative findings, all of which may improve surgical outcomes [52]. The ability to visualize patient-specific anatomy in three dimensions, rather than trying to craft a 3-D depiction utilizing two-dimensional imaging has clear benefits, especially when trying to understand the secondary changes that may accompany a large resection.

Similarly, neurosurgeons have utilized 3-D-printed models to better plan and avoid complications in complex surgical cases. One case study showed how a 3-D model changed the initial plan for operation in a patient with complex skull base and craniovertebral junction deformities; they were able to assess which approaches proved too dangerous, visualize aberrant neurovasculature, and better understand and pre-emptively plan for intraoperative complications [84]. 3D preoperative planning has also grown within spine surgery where personalized models have been shown to reduce blood loss and intraoperative time while eliminating pedicle screw penetrations and misplacements in patients with complex spinal disorders [85].

In cardiothoracic surgery, the use of 3-D printing has skyrocketed within the past decade, and its application within preoperative planning has been widely utilized. Its use has found success in a myriad of cases, but most prominently when planning for primary tumor resection, for aberrant vasculature, and for correction of complex congenital heart defects, especially with intracardiac baffles [86–90]. The 3-D modeling guides each surgeon in correctly choosing an informed surgical plan,

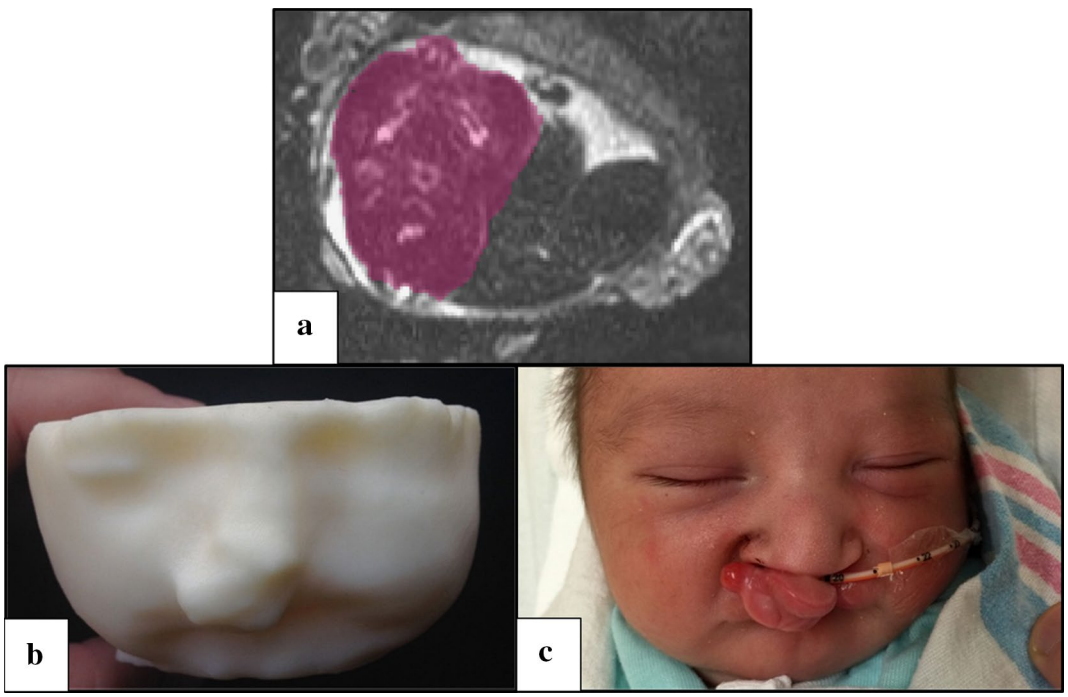

Figure 3: (a) MRI showing unclear evidence of airway obstruction in a fetus with known congenital malformation of the maxillofacial area; (b) Final 3-D-printed model that demonstrates an isolated upper lip soft tissue mass not involving the airway of the fetus; (c) Patient delivered successfully via cesarean section without need for emergency ex utero intrapartum treatment (EXIT) procedure given 3-D model demonstration of clear airway.

particularly in these more challenging and atypical anatomical representations, in a way that may be more beneficial than conventional cross-sectional imaging.

3-D printing has also gained traction in craniofacial surgery, as the wide-ranging anatomical variations in head and neck anatomy renders any surgery both daunting and potentially disfiguring. The utmost importance must be placed on fine manipulation to help mitigate potential complications, and 3-D printing allows one to create more representative models that provide more predictable results [91–95]. Models have been utilized in orbital reconstructive surgery, wherein the titanium replacement plate is morphed to exact anatomical parameters by using the 3-D-printed model, which can potentially improve outcomes and can reduce surgery time [96–98]. More widely known is 3-D printing's application in mandibular and maxilla reconstructive surgeries, wherein new grafts can be similarly pre-bent and sculpted to the original anatomy, or the 3-D patient models can be constructed to mirror the opposing anatomy and ultimately also decrease intraoperative timing [99–101]. Among others, there is further utility in otolaryngology for OSA [102], auricular scaffolds [103], nasal septal perforation and scaffolding [104], and in skull-based surgery [71]. As a wide-ranging preoperative tool, 3D printing remains well integrated into many fields including plastic surgery, urology, orthopedics, and hepatobiliary surgery among many others helping to depict and better navigate abnormal anatomy for favorable patient outcomes [105–108].

Personalized devices & therapies

The implementation of 3-D printing for surgical applications has ushered in a variety personalized therapies and devices now offered to patients. The first reported 3-D-printed medical device was a successful lifesaving bioabsorbable tracheobronchial splint used in an infant in critical condition with bronchomalacia to help maintain a patent airway [109]. The use of these PSI's, has become increasingly utilized across a number of surgical fields with a myriad of potential applications [1]. PSIs can be described as precisely fitted implants that allow for the restoration of sound anatomy and function generated through the use of patient-specific 3-D design and, typically, 3-D printing. For example, PSIs in craniomaxillofacial surgery include titanium implants that can be combined with autogenous bone grafts for reconstruction of mandibles with integrated dental implants, as well as polyether ether ketone ketone (PEKK) implants that have been developed for restoration/reconstruction of traumatic or genetic zygomatico-orbital and mandibular defects [110]. PSIs have also been used in orthopedic surgery for reconstruction of certain bony features following resection of tumors, as external fixators used in treating fractures, and in cervical spine restoration [111–114]. The use of PSIs is becoming more widespread, and their utility can be observed in many more surgical fields such as thoracic surgery, neurosurgery, ophthalmology, and vascular surgery [85, 115, 116, 117, 118].

These custom-fit models allow surgeons to more aptly fit prosthesis, create customized surgical equipment, and employ customizable surgical guides, with the goal of improving patient care. Patient-specific treatments have been utilized in orthopedic surgery [119–123], and with personalized screw fixations [124]; these advancements have not only improved surgeon ease but have resulted in shorter time in the operating room and less operative blood loss. Another study discussed upper limb prosthetics and how 3-D-printed prosthesis are attractive for both their affordability and customizability [125].

Custom fit devices have been widely used within the oral maxillofacial surgery section as surgical guides are already common devices. Patient-specific devices have been sought after for mandibular free flap reconstruction, genioplasties, maxillary fractures and mandibular osteotomies among various other surgical procedures [25, 126, 127, 128]. More innovative prints have come in the forms of customizable BiPAP/CPAP devices, tegmen prosthesis, and personalized trachea plugs. BiPAP and CPAP devices are widely used to help treat obstructive sleep apnea (OSA), and in neuromuscular disorders that hinder respiratory strength, such as Myasthenia Gravis (MG) or amyotrophic lateral sclerosis (ALS). The traditional masks lack customization and are subjectively described as being uncomfortable, poor fitting, commonly allow for air leakage, and can even trigger claustrophobia in some patients [129]. With continued frustration, patients elect to discontinue their use, and ultimately, the intended treatment cannot be delivered. One study examined the effects of custom fitting BiPAP/CPAP for one patient; the participant described improvement in the majority of the custom-made masks, and most notably noted the comfortability of the fits [130]. These findings, though only in a single patient study, are promising and pave the way for future use in creating comfortable, appropriate masks that are easy for patients to use consistently. When CPAP machines are unable to be tolerated, mandibular advancement devices (MAD) can be a worthwhile alternative. Similar to conventional CPAP machines, traditional MAD devices are viewed as being uncomfortable, and oftentimes cause a chronic gag response [131]. 3-D-printed customizable devices have been shown in case studies to improve diagnostic PSG values, and decrease apnea/hypopnea index (AHI) per hour; almost more importantly, the patient was adherent to the treatment after being unable to tolerate his normal CPAP machine [102].

Customized tegmen plates for lateral skull base defects have shown considerable improvement over their conventional counterparts. In one study, 3-D personalized models cut the intraoperative placement time from nearly 60 min to less than 1 min; the high attention to detail enabled the surgeons to avoid key

surrounding structures, and quickly adhere the plate to the temporal bone surface [132]. Moreover, another study found that customizable tegmen devices adequately covered the deficits, without any additional intraoperative modifications or temporal lobe manipulation, and all five patients had no encountered complications; this model is detailed in Fig. 4 [133]. As an in-house printing program further expands, the options of what an institution desires to print is limited only by the imagination and innovation of the multidisciplinary team in place.

One of the most exciting and novel applications of 3-D printing, and specifically, the implementation of an in-house printing infrastructure, is the ability to respond to new and pressing challenges, most recently illustrated by the concerns of COVID-19. Worldwide shortages in adequate PPE and ventilator availability proved fatal for many patients, while scarcity of adequate nasal swabs proved a formidable task for widespread testing; 3-D printing has been helpful in all three regards. Common PPE used to protect healthcare workers include contact and respiratory droplet protective gowns, N95 masks, eye protection, and respiratory protection during aerosol generating procedures among other important pieces of equipment. Local in-house 3-D production of PPE that does not rely on the traditional supply chain allows an institution to circumvent the shortage on many of these products. One study examined the use of 3-D printing and found that 3-D-printed reusable masks that were subsequently widely distributed to the community and face shields are among the most popular products processed [26]. Equally if not more important is the addition of 3-D-printed ventilator splitting mechanisms. Ventilators are used for the sickest patients, and there are a finite number of ventilators available in each hospital [134]. 3-D-printed ventilators were able to split and individually adhere to each patient's ventilator requirements, allowing it to address the rapid increase in need for these life saving devices. Though these ventilators have yet to be commercially implemented, one study examined the utility with over 200 million computer simulation. The examiners were about to identify and mitigate the difference in delivered airflow volume, helping to avoid barotrauma, and examined viral and bacterial cross-contamination. They ultimately concluded that under dire circumstances, at least in principle, the ventilator splitter and resistor system (VSRS) be used to split a ventilator among two patients [135]. This technology is not only reserved for COVID-19 concerns but was thought to possibly be eventually utilized in other respiratory outbreaks, underequipped ICU units, and even during critical warfare situations. One such model produced by the University of Michigan is shown in Fig. 5.

Finally, nasopharyngeal swabs used for analytical testing remain important not only to monitor the progression of COVID-19 throughout the world, but also to determine when

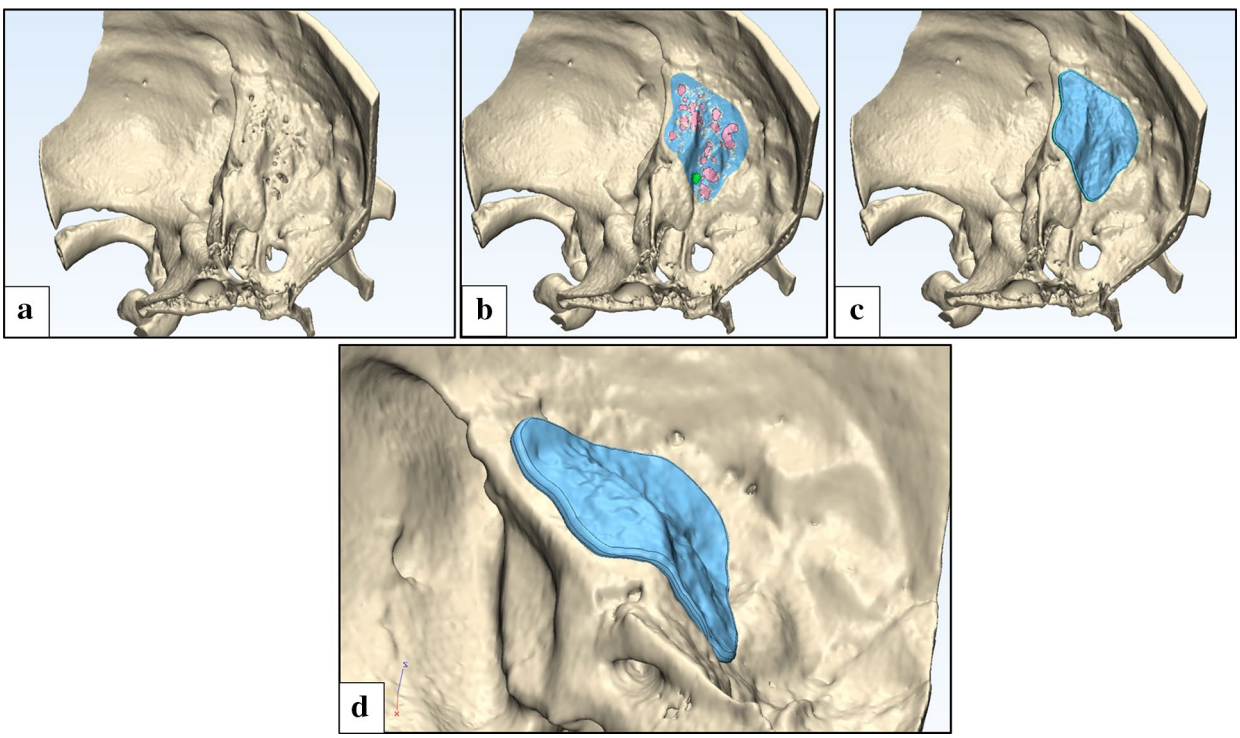

Figure 4: (a) 3-D-printed model of the patient's temporal bone depicting various deformities; (b) Deformities are shown in pink with proposed tegmen plate reconstruction overlaying the defects in blue; (c) Tegmen plate reconstruction overlaying the deformity; (d) Tegmen plate matching the specific patient anatomy.

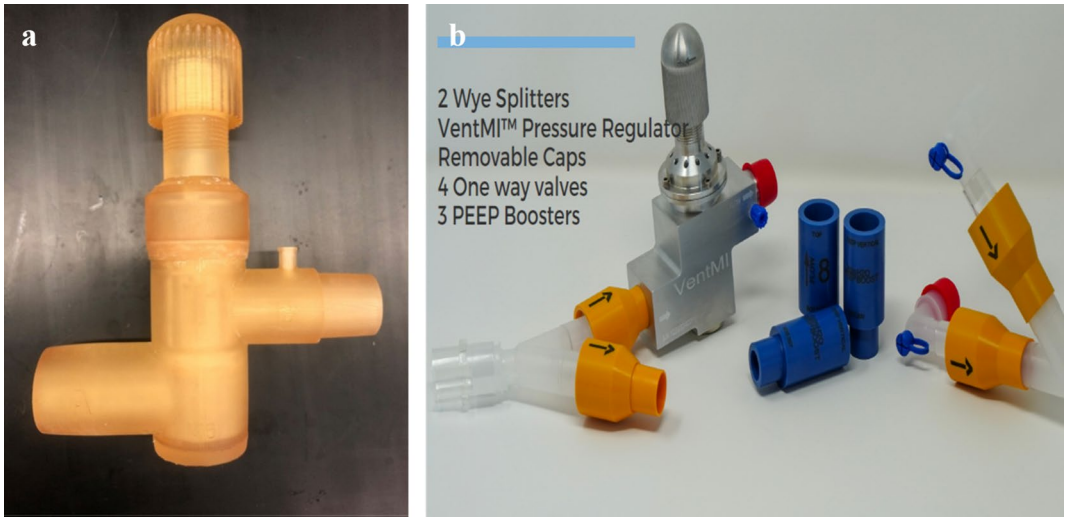

Figure 5: (a) 3-D-printed split VentMI ventilation model; (b) Complete set of VentMI split ventilation pieces ready for clinical use.

restrictions on daily living may be alleviated. 3-D-printed nasal swabs not only were able to help ease the burden and lack of supply, but outperformed conventional swabs with regard to sample retention while improving patient comfort [136]. Similarly, another study noted improved comfort with the 3-D-printed nasal swabs, engineering each swab to shrink while under axial tension, and thus better navigate through the nares [137]. Both studies exemplified the strength of 3-D printing and its ability to respond to rapidly changing environments, such as future pandemics.

With the implementation of an in-house, self-sufficient, 3-D printing program, expanding its use for any number of relevant applications becomes readily available: further assistance in the operating room through intraoperative and surgical simulation models, constructing custom-fit devices, and responding to novel challenges that need not rely on central government sources such as the COVID-19 crisis, are all within the realm of possibility.

Future applications

There are several complex areas of research in 3-D printing that allow for the integration of human biology with highly complex printed 3-D structures. The technologies around 3-D printing allow for intricate design configurations, scaffolds and geometries that are otherwise not possible with conventional manufacturing. This will ultimately contribute to more personalized and improved methods for medicine and surgical care of patients [138, 139]. Bionics, which integrate functioning electronic devices into 3-D-printed implants, is one such area of application [140]. By far the main bionic that has been successfully produced and used successfully is the human bionic ear [141]. For example, a group out of Princeton University successfully 3-D-printed a human ear that contained chondrocytes layered on a scaffold of biomaterial and combined this with silver nanoparticles that functioned as a coil antenna [141]. The antenna could receive radiofrequency signals and thus turned this static 3-D print into a functioning human structure [64, 132].

Furthermore, tissue engineering—a technique used to generate replacement of tissue in vitro that can be incorporated into the human body—and regenerative medicine—a process of using stem cell technology to restore normal structure and function to various anatomical components—are other areas of emerging application that have both been demonstrated to be successfully executed through the use of 3-D printing [27]. For these processes, three-dimensional printers are utilized to produce specific scaffolding structures that align with patient-specific anatomical features, while maintaining microscopic design features that maximize cellular activity and function. These scaffolds are then implanted with living stem cells and tissue components. For example, Zopf et al.successfully 3-D-printed a nasal and ear scaffold layered in chondrogenic growth factors that led to cartilage growth and Chang et al.3-D-printed a bio-scaffold implanted with mesenchymal stem cells that grew into tracheas used in rabbits [103, 109, 142].

Finally, bioprinting—the ability to print 2-Dimensional (2-D) and 3-D tissues and organs—is another area of rapidly emerging research and offers many advantages over tissue engineering and regenerative medicine such as higher resolution, increased concentration of cells and cell placement, and more accurate cell placement. 3-D printing is well suited for bioprinting as it allows to produce cells and biomaterials

integrated with cells and can then layer these materials in unique 3-D dimensional fashions to match human tissue and organs. Excitingly, bioprinting has already been demonstrated to be successful in printing knee menisci's, heart valves, auricular and articular cartilage, and an artificial liver, and its use may continue to improve many other areas in medicine [143–145]. In transplant surgery, for example, the use of bioprinted organs from the stem cells of the patient reduces the risk of rejection and could increase the number of recipients of transplantation, given the shortage of organs in the United States (U.S.) [27, 145, 146]. However, the printing of complex organs such as hearts and kidneys that can function *in vivo,* represents the pinnacle and confluence of several technologies. While exciting progress is being made, it appears we are still years away from realizing this dream due to the challenges of printing interwoven vascular networks and replication of advanced human physiology [6, 147].

3-D printing can not only be useful in surgical applications, but also in medical therapies that involve the development of novel 3-D-printed dosage forms such as microcapsules with antibiotic printed micropattern and mesoporous bioactive glass scaffolds that challenge the existing drug formulations [138]. Furthermore, 3-D printing has led to the development of intricate drug release profiles (i.e., matrix powder layers that regulate timing and dose of drug release) and customized drug delivery devices (i.e., multilayered bone implant scaffold that alternates antibiotic release for treating bone infections) [6, 148, 149]. These applications offer exciting areas of research and development for future revolutions in pharmaceutical therapies.

Each application listed highlights an exciting and revolutionary advancement in medicine but may be prohibited due to the time spent or cost of each print. Many major medical centers are now investigating how an in-house 3-D modeling system and workflow can be perfected to overcome some of these logistically difficult barriers, and what steps need to be taken to increase 3-D printing's availability.

Conclusion

In this paper, we have described the necessary considerations for establishing a clinical point-of-care additive manufacturing system and workflow. From the materials and resources involved in additive manufacturing, to the digital workflow, regulatory guidelines, and assemblance of collaborative multidisciplinary teams, the establishment of a successful centralized in-house system is complex yet realistic with the guidance provided in this paper. Furthermore, we have outlined a myriad of both current and future uses of 3-D printing in medicine; as the technology of 3-D printing continues to advance, the number of available applications will simultaneously follow lead, and an in-house printing program will prove invaluable.3-D printing is changing the landscape of medicine beyond just the biomedical sciences. We hope to motivate capable institutions to adopt similar in-house models.

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Availability of data and material

Data will be made available on reasonable request.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Consent to participate

Informed consent was obtained from all individual participants included in this study.

Consent for publication

We, the authors, give our consent for publication.

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