

Medical Applications for 3D Printing: Current and Projected Uses

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INTRODUCTION

Medical applications for 3D printing are expanding rapidly and are expected to revolutionize health care.¹ Medical uses for 3D printing, both actual and potential, can be organized into several broad categories, including: tissue and organ fabrication; creation of customized prosthetics, implants, and anatomical models; and pharmaceutical research regarding drug dosage forms, delivery, and discovery.² The application of 3D printing in medicine can provide many benefits, including: the customization and personalization of medical products, drugs, and equipment; cost-effectiveness; increased productivity; the democratization of design and manufacturing; and enhanced collaboration.^{1,3-6} However, it should be cautioned that despite recent significant and exciting medical advances involving 3D printing, notable scientific and regulatory challenges remain and the most transformative applications for this technology will need time to evolve.^{3-5,7}

WHAT IS 3D PRINTING?

Three-dimensional (3D) printing is a manufacturing method in which objects are made by fusing or depositing materials—such as plastic, metal, ceramics, powders, liquids, or even living cells—in layers to produce a 3D object.^{1,8,9} This process is also referred to as additive manufacturing (AM), rapid prototyping (RP), or solid free-form technology (SFF).⁶ Some 3D printers are similar to traditional inkjet printers; however, the end product differs in that a 3D object is produced.¹ 3D printing is expected to revolutionize medicine and other fields, not unlike the way the printing press transformed publishing.¹

There are about two dozen 3D printing processes, which use varying printer technologies, speeds, and resolutions, and hundreds of materials.⁹ These technologies can build a 3D object in almost any shape imaginable as defined in a computer-aided design (CAD) file (Figure 1).⁹ In a basic setup, the 3D printer first follows the instructions in the CAD file to build the foundation for the object, moving the printhead along the x-y plane.⁵ The printer then continues to follow the instructions, moving the printhead along the z-axis to build the object vertically layer by layer.⁵ It is important to note that two-dimensional (2D) radiographic images, such as x-rays, magnetic resonance imaging (MRI), or computerized tomography (CT) scans, can be converted to digital 3D print

files, allowing the creation of complex, customized anatomical and medical structures (Figure 2).^{3,5,10}

THE HISTORY OF 3D PRINTING

Charles Hull invented 3D printing, which he called “stereolithography,” in the early 1980s.¹ Hull, who has a bachelor’s degree in engineering physics, was working on making plastic objects from photopolymers at the company Ultra Violet Products in California.⁶ Stereolithography uses an .stl file format to interpret the data in a CAD file, allowing these instructions to be communicated electronically to the 3D printer.⁶ Along with shape, the instructions in the .stl file may also include information such as the color, texture, and thickness of the object to be printed.⁶

Hull later founded the company 3D Systems, which developed the first 3D printer, called a “stereolithography apparatus.”⁶ In 1988, 3D Systems introduced the first commercially available 3D printer, the SLA-250.⁶ Many other companies have since developed 3D printers for commercial applications, such as DTM Corporation, Z Corporation, Solidscape, and Objet Geometries.⁶ Hull’s work, as well as advances made by other researchers, has revolutionized manufacturing, and is poised to do the same in many other fields—including medicine.⁶

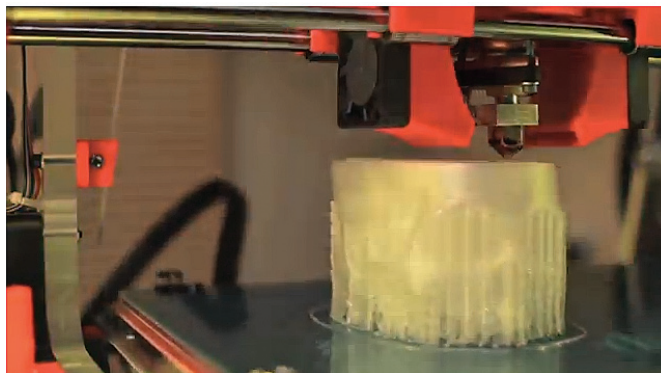


Figure 1 A 3D printer uses instructions in a digital file to create a physical object.¹²

OVERVIEW OF CURRENT APPLICATIONS

Commercial Uses

3D printing has been used by the manufacturing industry for decades, primarily to produce product prototypes.^{1,9} Many manufacturers use large, fast 3D printers called “rapid prototyping machines” to create models and molds.¹¹ A large number of .stl files are available for commercial purposes.¹ Many of these printed objects are comparable to traditionally manufactured items.¹

Companies that use 3D printing for commercial medical applications have also emerged.² These include: Helisis, Ultimateker, and Organovo, a company that uses 3D printing to fabricate living human tissue.² At present, however, the impact of 3D printing in medicine remains small.¹ 3D printing is currently a \$700 million industry, with only \$11 million (1.6%) invested in medical applications.¹ In the next 10 years, however, 3D printing is expected to grow into an \$8.9 billion industry, with \$1.9 billion (21%) projected to be spent on medical applications.¹

Disclosures: The author reports no commercial or financial relationships in regard to this article.

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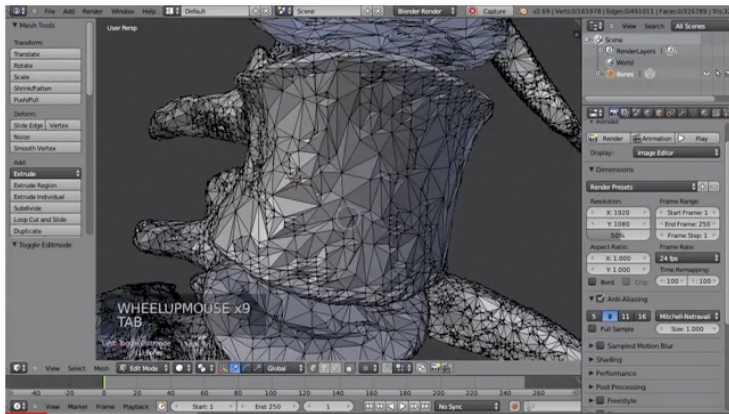


Figure 2 Radiographic images can be converted to 3D print files to create complex, customized anatomical and medical structures.¹²

Consumer Uses

3D printing technology is rapidly becoming easy and inexpensive enough to be used by consumers.^{9,11} The accessibility of downloadable software from online repositories of 3D printing designs has proliferated, largely due to expanding applications and decreased cost.^{2,4,11} It is now possible to print anything, from guns, clothing, and car parts to designer jewelry.² Thousands of premade designs for 3D items are available for download, many of them for free.¹¹

Since 2006, two open-source 3D printers have become available to the public, Fab@Home (www.fabathome.org) and RepRap (www.reprap.org/wiki/RepRap).^{6,9} The availability of these open-source printers greatly lowered the barrier of entry for people who want to explore and develop new ideas for 3D printing.⁹ These open-source systems allow anyone with a budget of about \$1,000 to build a 3D printer and start experimenting with new processes and materials.⁹

This low-cost hardware and growing interest from hobbyists has spurred rapid growth in the consumer 3D printer market.¹¹ A relatively sophisticated 3D printer costs about \$2,500 to \$3,000, and simpler models can be purchased for as little as \$300 to \$400.^{8,11} For consumers who have difficulty printing 3D models themselves, several popular 3D printing services have emerged, such as Shapeways, (www.shapeways.com), Thingiverse (www.thingiverse.com), MyMiniFactory (www.myminifactory.com), and Threeding (www.threeding.com).¹¹

COMMON TYPES OF 3D PRINTERS

All 3D printing processes offer advantages and disadvantages.³ The type of 3D printer chosen for an application often depends on the materials to be used and how the layers in the finished product are bonded.¹¹ The three most commonly used 3D printer technologies in medical applications are: selective laser sintering (SLS), thermal inkjet (TIJ) printing, and fused deposition modeling (FDM).^{10,11} A brief discussion of each of these technologies follows.

Selective Laser Sintering

An SLS printer uses powdered material as the substrate for printing new objects.¹¹ A laser draws the shape of the object in the powder, fusing it together.¹¹ Then a new layer of powder is laid down and the process repeats, building each layer, one by

one, to form the object.¹¹ Laser sintering can be used to create metal, plastic, and ceramic objects.¹¹ The degree of detail is limited only by the precision of the laser and the fineness of the powder, so it is possible to create especially detailed and delicate structures with this type of printer.¹¹

Thermal Inkjet Printing

Inkjet printing is a “noncontact” technique that uses thermal, electromagnetic, or piezoelectric technology to deposit tiny droplets of “ink” (actual ink or other materials) onto a substrate according to digital instructions.¹⁰ In inkjet printing, droplet deposition is usually done by using heat or mechanical compression to eject the ink drops.¹⁰ In TIJ printers, heating the printhead creates small air bubbles that collapse, creating pressure pulses that eject ink drops from nozzles in volumes as small as 10 to 150 picoliters.¹⁰ Droplet size can be varied by adjusting the applied temperature gradient, pulse frequency, and ink viscosity.¹⁰

TIJ printers are particularly promising for use in tissue engineering and regenerative medicine.^{10,13} Because of their digital precision, control, versatility, and benign effect on mammalian cells, this technology is already being applied to print simple 2D and 3D tissues and organs (also known as bioprinting).¹⁰ TIJ printers may also prove ideal for other sophisticated uses, such as drug delivery and gene transfection during tissue construction.¹⁰

Fused Deposition Modeling

FDM printers are much more common and inexpensive than the SLS type.¹¹ An FDM printer uses a printhead similar to an inkjet printer.¹¹ However, instead of ink, beads of heated plastic are released from the printhead as it moves, building the object in thin layers.^{4,11} This process is repeated over and over, allowing precise control of the amount and location of each deposit to shape each layer.⁴ Since the material is heated as it is extruded, it fuses or bonds to the layers below.⁴ As each layer of plastic cools, it hardens, gradually creating the solid object as the layers build.¹¹ Depending on the complexity and cost of an FDM printer, it may have enhanced features such as multiple printheads.¹¹ FDM printers can use a variety of plastics.¹¹ In fact, 3D FDM printed parts are often made from the same thermoplastics that are used in traditional injection molding or machining, so they have similar stability, durability, and mechanical properties.⁴

BENEFITS OF 3D PRINTING IN MEDICAL APPLICATIONS

Customization and Personalization

The greatest advantage that 3D printers provide in medical applications is the freedom to produce custom-made medical products and equipment.³ For example, the use of 3D printing to customize prosthetics and implants can provide great value for both patients and physicians.³ In addition, 3D printing can produce made-to-order jigs and fixtures for use in operating rooms.⁴ Custom-made implants, fixtures, and surgical tools can have a positive impact in terms of the time required for surgery, patient recovery time, and the success of the surgery

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or implant.⁴ It is also anticipated that 3D printing technologies will eventually allow drug dosage forms, release profiles, and dispensing to be customized for each patient.⁵

Increased Cost Efficiency

Another important benefit offered by 3D printing is the ability to produce items cheaply.¹ Traditional manufacturing methods remain less expensive for large-scale production; however, the cost of 3D printing is becoming more and more competitive for small production runs.¹ This is especially true for small-sized standard implants or prosthetics, such as those used for spinal, dental, or craniofacial disorders.³ The cost to custom-print a 3D object is minimal, with the first item being as inexpensive as the last.¹ This is especially advantageous for companies that have low production volumes or that produce parts or products that are highly complex or require frequent modifications.⁴

3D printing can also reduce manufacturing costs by decreasing the use of unnecessary resources.⁵ For example, a pharmaceutical tablet weighing 10 mg could potentially be custom-fabricated on demand as a 1-mg tablet.⁵ Some drugs may also be printed in dosage forms that are easier and more cost-effective to deliver to patients.⁵

Enhanced Productivity

“Fast” in 3D printing means that a product can be made within several hours.⁴ That makes 3D printing technology much faster than traditional methods of making items such as prosthetics and implants, which require milling, forging, and a long delivery time.³ In addition to speed, other qualities, such as the resolution, accuracy, reliability, and repeatability of 3D printing technologies, are also improving.³

Democratization and Collaboration

Another beneficial feature offered by 3D printing is the democratization of the design and manufacturing of goods.⁴ An increasing array of materials is becoming available for use in 3D printing, and they are decreasing in cost.⁴ This allows more people, including those in medical fields, to use little more than a 3D printer and their imaginations to design and produce novel products for personal or commercial use.⁴

The nature of 3D printing data files also offers an unprecedented opportunity for sharing among researchers.⁶ Rather than trying to reproduce parameters that are described in

scientific journals, researchers can access downloadable .stl files that are available in open-source databases.⁶ By doing so, they can use a 3D printer to create an exact replica of a medical model or device, allowing the precise sharing of designs.⁶ Toward this end, the National Institutes of Health established the 3D Print Exchange (3dprint.nih.gov) in 2014 to promote open-source sharing of 3D print files for medical and anatomical models, custom labware, and replicas of proteins, viruses, and bacteria (Figure 3).¹²

MEDICAL APPLICATIONS FOR 3D PRINTING

3D printing has been applied in medicine since the early 2000s, when the technology was first used to make dental implants and custom prosthetics.^{6,10} Since then, the medical applications for 3D printing have evolved considerably. Recently published reviews describe the use of 3D printing to produce bones, ears, exoskeletons, windpipes, a jaw bone, eyeglasses, cell cultures, stem cells, blood vessels, vascular networks, tissues, and organs, as well as novel dosage forms and drug delivery devices.^{1,3,11} The current medical uses of 3D printing can be organized into several broad categories: tissue and organ fabrication; creating prosthetics, implants, and anatomical models; and pharmaceutical research concerning drug discovery, delivery, and dosage forms.² A discussion of these medical applications follows.

Bioprinting Tissues and Organs

Tissue or organ failure due to aging, diseases, accidents, and birth defects is a critical medical problem.¹⁰ Current treatment for organ failure relies mostly on organ transplants from living or deceased donors.¹⁰ However, there is a chronic shortage of human organs available for transplant.^{1,10} In 2009, 154,324 patients in the U.S. were waiting for an organ.¹⁰ Only 27,996 of them (18%) received an organ transplant, and 8,863 (25 per day) died while on the waiting list.¹⁰ As of early 2014, approximately 120,000 people in the U.S. were awaiting an organ transplant.¹ Organ transplant surgery and follow-up is also expensive, costing more than \$300 billion in 2012.¹⁰ An additional problem is that organ transplantation involves the often difficult task of finding a donor who is a tissue match.¹ This problem could likely be eliminated by using cells taken from the organ transplant patient's own body to build a replacement organ.^{1,13} This would minimize the risk of tissue rejection, as well as the need to take lifelong immunosuppressants.^{1,13}

Therapies based on tissue engineering and regenerative medicine are being pursued as a potential solution for the organ donor shortage.^{1,10} The traditional tissue engineering strategy is to isolate stem cells from small tissue samples, mix them with growth factors, multiply them in the laboratory, and seed the cells onto scaffolds that direct cell proliferation and differentiation into functioning tissues.^{7,10,13} Although still in its infancy, 3D bioprinting offers additional important advantages beyond this traditional regenerative method (which essentially provides scaffold support alone), such as: highly precise cell placement and high digital control of speed, resolution, cell concentration, drop volume, and diameter of printed cells.^{10,13} Organ printing takes advantage of 3D printing technology to produce cells, biomaterials, and cell-laden biomaterials individually or in tandem, layer by layer, directly creating 3D

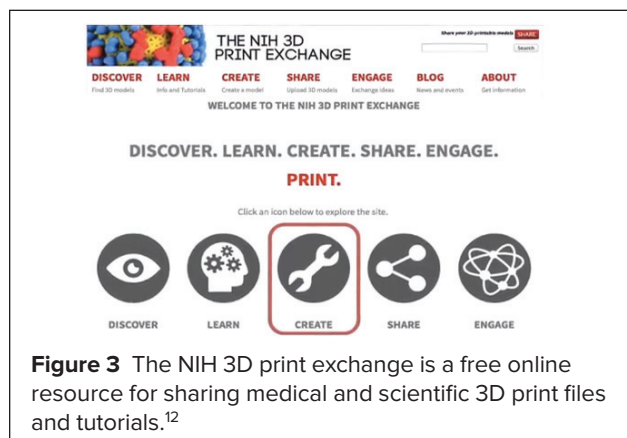


Figure 3 The NIH 3D print exchange is a free online resource for sharing medical and scientific 3D print files and tutorials.¹²

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tissue-like structures.¹³ Various materials are available to build the scaffolds, depending on the desired strength, porosity, and type of tissue, with hydrogels usually considered to be most suitable for producing soft tissues.^{6,7}

Although 3D bioprinting systems can be laser-based, inkjet-based, or extrusion-based, inkjet-based bioprinting is most common.¹³ This method deposits “bioink,” droplets of living cells or biomaterials, onto a substrate according to digital instructions to reproduce human tissues or organs.¹³ Multiple printheads can be used to deposit different cell types (organ-specific, blood vessel, muscle cells), a necessary feature for fabricating whole heterocellular tissues and organs.¹³ A process for bioprinting organs has emerged: 1) create a blueprint of an organ with its vascular architecture; 2) generate a bioprinting process plan; 3) isolate stem cells; 4) differentiate the stem cells into organ-specific cells; 5) prepare bioink reservoirs with organ-specific cells, blood vessel cells, and support medium and load them into the printer; 6) bioprint; and 7) place the bioprinted organ in a bioreactor prior to transplantation.¹³ Laser printers have also been employed in the cell printing process, in which laser energy is used to excite the cells in a particular pattern, providing spatial control of the cellular environment.¹³

Although tissue and organ bioprinting is still in its infancy, many studies have provided proof of concept. Researchers have used 3D printers to create a knee meniscus, heart valve, spinal disk, other types of cartilage and bone, and an artificial ear.^{4,6,7} Cui and colleagues applied inkjet 3D printing technology to repair human articular cartilage.¹³ Wang et al used 3D bioprinting technology to deposit different cells within various biocompatible hydrogels to produce an artificial liver.¹³ Doctors at the University of Michigan published a case study in the *New England Journal of Medicine* reporting that use of a 3D printer and CT images of a patient’s airway enabled them to fabricate a precisely modeled, bioresorbable tracheal splint that was surgically implanted in a baby with tracheobronchomalacia.⁷ The baby recovered, and full resorption of the splint is expected to occur within three years.⁷

A number of biotech companies have focused on creating tissues and organs for medical research.⁷ It may be possible to rapidly screen new potential therapeutic drugs on patient tissue, greatly cutting research costs and time.¹ Scientists at Organovo are developing strips of printed liver tissue for this purpose; soon, they expect the material will be advanced enough to use in screening new drug treatments.⁷ Other researchers are working on techniques to grow complete human organs that can be used for screening purposes during drug discovery.⁶ An organ created from a patient’s own stem cells could also be used to screen treatments to determine if a drug will be effective for that individual.³

Challenges in Building 3D Vascularized Organs

Proof-of-concept studies regarding bioprinting have been performed successfully, but the organs that have been produced are miniature and relatively simple.^{1,9,10} They are also often avascular, aneural, alymphatic, thin, or hollow, and are nourished by the diffusion from host vasculature.^{1,6,9,10} However, when the thickness of the engineered tissue exceeds 150–200 micrometers, it surpasses the limitation for oxygen diffusion between host and transplanted tissue.¹⁰ As a result,

bioprinting complex 3D organs will require building precise multicellular structures with vascular network integration, which has not yet been done.⁶

Most organs needed for transplantation are thick and complex, such as the kidney, liver, and heart.¹¹ Cells in these large organ structures cannot maintain their metabolic functions without vascularization, which is normally provided by blood vessels.¹³ Therefore, functional vasculature must be bioprinted into fabricated organs to supply the cells with oxygen/gas exchange, nutrients, growth factors, and waste-product removal—all of which are needed for maturation during perfusion.^{10,13} Although the conventional tissue engineering approach is not now capable of creating complex vascularized organs, bioprinting shows promise in resolving this critical limitation.¹⁰ The precise placement of multiple cell types is required to fabricate thick and complex organs, and for the simultaneous construction of the integrated vascular or microvascular system that is critical for these organs to function.¹⁰

TIJ printers are considered to be the most promising for this use. However, various 3D printing techniques and materials have been applied successfully to create vasculature as simple as a single channel, as well as more complex geometries, such as bifurcated or branched channels.^{6,10,13} Recently, collaborators from a network of academic institutions, including the University of Sydney, Harvard University, Stanford University, and the Massachusetts Institute of Technology, announced that they had bioprinted a functional and perfusable network of capillaries, an achievement that represents a significant stride toward overcoming this problem.¹⁴

Customized Implants and Prostheses

Implants and prostheses can be made in nearly any imaginable geometry through the translation of x-ray, MRI, or CT scans into digital .stl 3D print files.^{2,3,6} In this way, 3D printing has been used successfully in the health care sector to make both standard and complex customized prosthetic limbs and surgical implants, sometimes within 24 hours.^{3,7,9} This approach has been used to fabricate dental, spinal, and hip implants.³ Previously, before implants could be used clinically, they had to be validated, which is very time-consuming.³

The ability to quickly produce custom implants and prostheses solves a clear and persistent problem in orthopedics, where standard implants are often not sufficient for some patients, particularly in complex cases.³ Previously, surgeons had to perform bone graft surgeries or use scalpels and drills to modify implants by shaving pieces of metal and plastic to a desired shape, size, and fit.^{3,7} This is also true in neurosurgery: Skulls have irregular shapes, so it is hard to standardize a cranial implant.³ In victims of head injury, where bone is removed to give the brain room to swell, the cranial plate that is later fitted must be perfect.⁹ Although some plates are milled, more and more are created using 3D printers, which makes it much easier to customize the fit and design.³

There have been many other commercial and clinical successes regarding the 3D printing of prostheses and implants.^{2,3,6} A research team at the BIOMED Research Institute in Belgium successfully implanted the first 3D-printed titanium mandibular prosthesis.² The implant was made by using a laser to successively melt thin layers of titanium powders.² In 2013,

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Figure 4 Researchers at the National Library of Medicine generate digital files from clinical data, such as CT scans, that are used to make custom 3D-printed surgical and medical models.¹²

Oxford Performance Materials received FDA approval for a 3D-printed polyetherketoneketone (PEKK) skull implant, which was first successfully implanted that year.² Another company, LayerWise, manufactures 3D-printed titanium orthopedic, maxillofacial, spinal, and dental implants.⁶ An anatomically correct 3D-printed prosthetic ear capable of detecting electromagnetic frequencies has been fabricated using silicon, chondrocytes, and silver nanoparticles.⁶ There is a growing trend toward making 3D-printed implants out of a variety of metals and polymers, and more recently implants have even been printed with live cells.⁹

3D printing has already had a transformative effect on hearing aid manufacturing.³ Today, 99% of hearing aids that fit into the ear are custom-made using 3D printing.³ Everyone's ear canal is shaped differently, and the use of 3D printing allows custom-shaped devices to be produced efficiently and cost-effectively.³ The introduction of customized 3D-printed hearing aids to the market was facilitated by the fact that class I medical devices for external use are subject to fewer regulatory restrictions.³ Invisalign braces are another successful commercial use of 3D printing, with 50,000 printed every day.⁹ These clear, removable, 3D-printed orthodontic braces are custom-made and unique to each user.⁹ This product provides a good example of how 3D printing can be used efficiently and profitably to make single, customized, complex items.⁹

Anatomical Models for Surgical Preparation

The individual variances and complexities of the human body make the use of 3D-printed models ideal for surgical preparation (Figure 4).² Having a tangible model of a patient's anatomy available for a physician to study or use to simulate surgery is preferable to relying solely on MRI or CT scans, which aren't as instructive since they are viewed in 2D on a flat screen.⁶ The use of 3D-printed models for surgical training is also preferable to training on cadavers, which present problems with respect to availability and cost.³ Cadavers also often lack the appropriate pathology, so they provide more of a lesson in anatomy than a representation of a surgical patient.³

3D-printed neuroanatomical models can be particularly

helpful to neurosurgeons by providing a representation of some of the most complicated structures in the human body (Figure 5).² The intricate, sometimes obscured relationships between cranial nerves, vessels, cerebral structures, and skull architecture can be difficult to interpret based solely on radiographic 2D images.² Even a small error in navigating this complex anatomy can have potentially devastating consequences.² A realistic 3D model reflecting the relationship between a lesion and normal brain structures can be helpful in determining the safest surgical corridor and can also be useful for the neurosurgeon to rehearse challenging cases.² Complex spinal deformities can also be studied better through the use of a 3D model.² High-quality 3D anatomical models with the right pathology for training doctors in performing colonoscopies are also vital, since colorectal cancer is the second leading cause of cancer-related deaths in the U.S.^{3,15}

Although still largely exploratory, 3D-printed models have been used in numerous cases to gain insight into a patient's specific anatomy prior to a medical procedure.⁶ Pioneering surgeons at Japan's Kobe University Hospital have used 3D-printed models to plan liver transplantations.² They use replicas of a patient's organs to determine how to best carve a donor liver with minimal tissue loss to fit the recipient's abdominal cavity.² These 3D models are made of partially transparent, low-cost acrylic resin or polyvinyl alcohol—materials that have a water content and texture similar to living tissues, allowing a more realistic penetration by the surgical blades.²

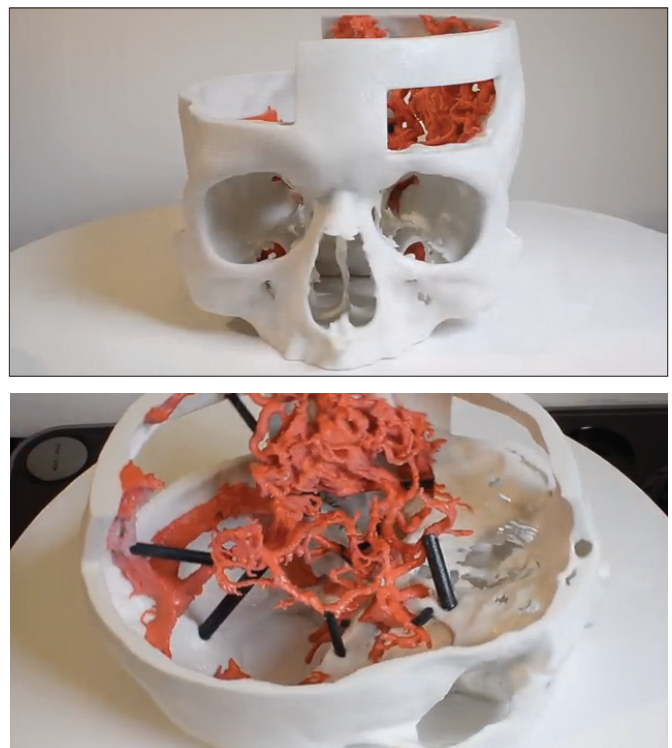


Figure 5 A 3D model used for surgical planning by neurosurgeons at the Walter Reed National Military Medical Center.¹²

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Other surgeons have used a 3D-printed model of a calcified aorta for surgical planning of plaque removal.⁶ A premature infant's airway was also reconstructed in order to study aerosol drug delivery to the lungs.⁶ It has been reported that an orthopedic surgery trainee used CT image scans and 3D modeling software to create print files representing a patient's bones.¹¹ The files were then sent to Shapeways to print custom models used for planning surgery.¹¹ The cost for 3D printing was a fraction of what it would normally cost to have custom models made, and the turn-around time was faster.¹¹

3D-printed models can be useful beyond surgical planning.⁶ Recently, a polypeptide chain model was 3D printed in such a way that it could fold into secondary structures because of the inclusion of bond rotational barriers and degrees of freedom considerations.⁶ Similar models could be utilized to aid the understanding of other types of biological or biochemical structures (Figure 6).⁶ Pre- and post-comprehension study results have shown that students are better able to conceptualize molecular structures when such 3D models are used.⁶

Custom 3D-Printed Dosage Forms and Drug Delivery Devices

3D printing technologies are already being used in pharmaceutical research and fabrication, and they promise to be transformative.⁵ Advantages of 3D printing include precise control of droplet size and dose, high reproducibility, and the ability to produce dosage forms with complex drug-release profiles.⁵

Complex drug manufacturing processes could also be stan-

that are formed into tablets through compression or molds.¹⁶ Each of these manufacturing steps can introduce difficulties, such as drug degradation and form change, possibly leading to problems with formulation or batch failures.¹⁶ In addition, these traditional manufacturing processes are unsuitable for creating personalized medicines and restrict the ability to create customized dosage forms with highly complex geometries, novel drug-release profiles, and prolonged stability.¹⁶

Personalized 3D-printed drugs may particularly benefit patients who are known to have a pharmacogenetic polymorphism or who use medications with narrow therapeutic indices.⁵ Pharmacists could analyze a patient's pharmacogenetic profile, as well as other characteristics such as age, race, or gender, to determine an optimal medication dose.⁵ A pharmacist could then print and dispense the personalized medication via an automated 3D printing system.⁵ If necessary, the dose could be adjusted further based on clinical response.⁵

3D printing also has the potential to produce personalized medicines in entirely new formulations—such as pills that include multiple active ingredients, either as a single blend or as complex multilayer or multireservoir printed tablets.¹⁶ Patients who have multiple chronic diseases could have their medications printed in one multidose form that is fabricated at the point of care.¹⁶ Providing patients with an accurate, personalized dose of multiple medications in a single tablet could potentially improve patient compliance.¹⁶ Ideally, compounding pharmacies could dispense 3D-printed drugs, since their customers are already familiar with purchasing customized medications.⁵

Unique Dosage Forms

The primary 3D printing technologies used for pharmaceutical production are inkjet-based or inkjet powder-based 3D printing.⁵ Whether another material or a powder is used as the substrate is what differentiates 3D inkjet printing from powder-based 3D inkjet printing.⁵

In inkjet-based drug fabrication, inkjet printers are used to spray formulations of medications and binders in small droplets at precise speeds, motions, and sizes onto a substrate.⁵ The most commonly used substrates include different types of cellulose, coated or uncoated paper, microporous bioceramics, glass scaffolds, metal alloys, and potato starch films, among others.⁵ Investigators have further improved this technology by spraying uniform "ink" droplets onto a liquid film that encapsulates it, forming microparticles and nanoparticles.⁵ Such matrices can be used to deliver small hydrophobic molecules and growth factors.⁵ In powder-based 3D printing drug fabrication, the inkjet printer head sprays the "ink" onto the powder foundation.⁵ When the ink contacts the powder, it hardens and creates a solid dosage form, layer by layer.⁵ The ink can include active ingredients as well as binders and other inactive ingredients.⁵ After the 3D-printed dosage form is dry, the solid object is removed from the surrounding loose powder substrate.⁵

These technologies offer the ability to create limitless dosage forms that are likely to challenge conventional drug fabrication.⁵ 3D printers have already been used to produce many novel dosage forms, such as: microcapsules, hyaluronan-based synthetic extracellular matrices, antibiotic printed micropatterns, mesoporous bioactive glass scaffolds, nanosuspensions, and multilayered drug delivery devices.⁵ Ink formulations used in

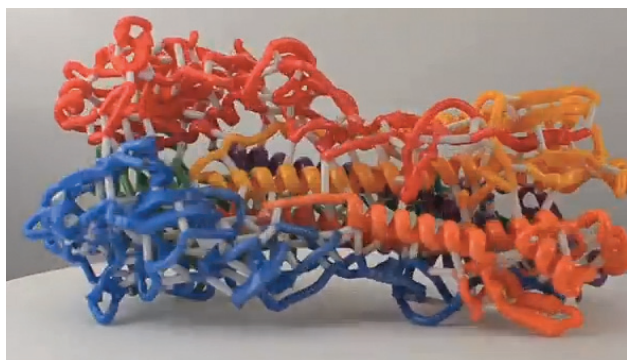


Figure 6 A 3D-printed representation of an influenza hemagglutinin trimer.¹²

dardized through use of 3D printing to make them simpler and more viable.³ 3D printing technology could be very important in the development of personalized medicine, too.³

Personalized Drug Dosing

The purpose of drug development should be to increase efficacy and decrease the risk of adverse reactions, a goal that can potentially be achieved through the application of 3D printing to produce personalized medications.^{3,5,16}

Oral tablets are the most popular drug dosage form because of ease of manufacture, pain avoidance, accurate dosing, and good patient compliance.¹⁶ However, no viable method is available that could routinely be used to make personalized solid dosage forms, such as tablets.¹⁶ Oral tablets are currently prepared via well-established processes such as mixing, milling, and dry and wet granulation of powdered ingredients

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3D drug printing have included a variety of active ingredients, such as: steroidal anti-inflammatory drugs, acetaminophen, theophylline, caffeine, vancomycin, ofloxacin, tetracycline, dexamethasone, paclitaxel, folic acid, and others.⁵ Inactive ingredients used in 3D drug printing have included: poly(lactico-glycolic acid), ethanol-dimethyl sulfoxide, surfactants (such as Tween 20), Kollidon SR, glycerin, cellulose, propylene glycol, methanol, acetone, and others.⁵

Complex Drug-Release Profiles

The creation of medications with complex drug-release profiles is one of the most researched uses of 3D printing.⁵ Traditional compressed dosage forms are often made from a homogeneous mixture of active and inactive ingredients, and are thus frequently limited to a simple drug-release profile.⁶ However, 3D printers can print binder onto a matrix powder bed in layers typically 200 micrometers thick, creating a barrier between the active ingredients to facilitate controlled drug release.⁶ 3D-printed dosage forms can also be fabricated in complex geometries that are porous and loaded with multiple drugs throughout, surrounded by barrier layers that modulate release.⁶

Implantable drug delivery devices with novel drug-release profiles can also be created using 3D printing.⁶ Unlike traditional systemic treatments that can affect nonaffected tissue, these devices can be implanted to provide direct treatment to the area involved.⁶ Bone infections are one example where direct treatment with a drug implant is more desirable than systemic treatment.⁶ Fortunately, powder-based 3D-printed bone scaffolding can be created in high-resolution models with complex geometries that mimic the natural bone extracellular matrix.⁵ The printing of medications with customized drug-release profiles into such bone implant scaffolds has been studied.⁵ One example is the printing of a multilayered bone implant with a distinct drug-release profile alternating between rifampicin and isoniazid in a pulse release mechanism.⁵ 3D printing has also been used to print antibiotic micropatterns on paper, which have been used as drug implants to eradicate *Staphylococcus epidermidis*.⁵

In other research concerning drug-release profiles, chlorpheniramine maleate was 3D printed onto a cellulose powder substrate in amounts as small as 10 to 12 moles to demonstrate that even a minute quantity of drug could be released at a specified time.⁵ This study displayed improved accuracy for the release of very small drug doses compared with conventionally manufactured medications.⁵ Dexamethasone has been printed in a dosage form with a two-stage release profile.⁵ Levofloxacin has been 3D printed as an implantable drug delivery device with pulsatile and steady-state release mechanisms.⁵

BARRIERS AND CONTROVERSIES

Unrealistic Expectations and Hype

Despite the many potential advantages that 3D printing may provide, expectations of the technology are often exaggerated by the media, governments, and even researchers.³ This promotes unrealistic projections, especially regarding how soon some of the more exciting possibilities—such as organ printing—will become a reality.³ Although progress is being made toward these and other goals, they are not expected to

happen soon.^{3,4} 3D printing will require vision, money, and time for the technology to evolve into the anticipated applications.³ While it is certain that the biomedical sector will be one of the most fertile fields for 3D printing innovations, it is important to appreciate what has already been achieved without expecting that rapid advances toward the most sophisticated applications will occur overnight.³

Safety and Security

3D printing has given rise to safety and security issues that merit serious concern.^{8,11} 3D printers have already been employed for criminal purposes, such as printing illegal items like guns and gun magazines, master keys, and ATM skimmers.^{7,11} These occurrences have highlighted the lack of regulation of 3D printing technology.⁷ In theory, 3D printing could also be used to counterfeit substandard medical devices or medications.¹² Although 3D printing should not be banned, its safety over the long term will clearly need to be monitored.⁷

In 2012, in response to the news that a functioning plastic handgun had been 3D printed, several local and state legislators introduced bills banning access to this technology.⁸ However, such fear-based policy responses could stifle the culture of openness necessary for 3D printing to thrive.⁸ Such a ban could push 3D printing underground at the expense of important scientific, medical, and other advances.⁸ There have already been reports of “garage biology” being conducted that could potentially lead to innovations in the life sciences.⁸ However, it is being conducted in secrecy to avoid interference from law enforcement—even though the research is legal.⁸

Patent and Copyright Concerns

Manufacturing applications of 3D printing have been subject to patent, industrial design, copyright, and trademark law for decades.¹¹ However, there is limited experience regarding how these laws should apply to the use of 3D printing by individuals to manufacture items for personal use, nonprofit distribution, or commercial sale.¹¹ Patents with a finite duration usually provide legal protection for proprietary manufacturing processes, composition of matter, and machines.¹¹ To sell or distribute a 3D-printed version of a patented item, a person would have to negotiate a license with the patent owner, since distribution of the item without permission would violate patent law.¹¹

Copyright is also an issue encountered in 3D printing.¹¹ The fact that copyrights traditionally don't apply to functional objects beyond their aesthetic value may limit the significance in this area.¹¹ However, that does not mean that concerns about copyrights are inconsequential.¹¹ In at least one case, a designer filed a copyright takedown notice demanding that a 3D print file repository remove another participant's design because the complainant considered the design to infringe on his copyright.¹¹

Regulatory Concerns

Securing approval from regulators is another significant barrier that may impede the widespread medical application of 3D printing.^{5,7} A number of fairly simple 3D-printed medical devices have received the FDA's 510(k) approval.¹⁷ However, fulfilling more demanding FDA regulatory requirements could be a hurdle that may impede the availability of 3D-printed medical products on a large scale.^{5,17} For example, the need

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for large randomized controlled trials, which require time and funding, could present a barrier to the availability of 3D-printed drug dosage forms.⁵ In addition, manufacturing regulations and state legal requirements could impose obstacles regarding the dispensing of 3D-printed medications.⁵ 3D drug printers must also be legally defined as manufacturing or compounding equipment to better determine what laws they are subject to.⁵

Ultimately, the regulatory decisions that are made should be based on sound science and technology.⁸ With this goal in mind, the FDA recently created a working group to assess technical and regulatory considerations regarding 3D printing.¹⁷ The FDA is also sponsoring a 3D printing workshop and webinar regarding technical considerations of 3D-printed medical devices, which will be held on October 8 and 9, 2014.^{17,18} Members of industry and academia have been invited to participate so that they may help shape future regulatory guidance.^{17,18}

FUTURE TRENDS

3D printing is expected to play an important role in the trend toward personalized medicine, through its use in customizing nutritional products, organs, and drugs.^{3,9} 3D printing is expected to be especially common in pharmacy settings.⁵ The manufacturing and distribution of drugs by pharmaceutical companies could conceivably be replaced by emailing databases of medication formulations to pharmacies for on-demand drug printing.¹ This would cause existing drug manufacturing and distribution methods to change drastically and become more cost-effective.¹ If most common medications become available in this way, patients might be able to reduce their medication burden to one polypill per day, which would promote patient adherence.⁵

The most advanced 3D printing application that is anticipated is the bioprinting of complex organs.^{3,11} It has been estimated that we are less than 20 years from a fully functioning printable heart.⁸ Although, due to challenges in printing vascular networks, the reality of printed organs is still some way off, the progress that has been made is promising.^{3,7} As the technology advances, it is expected that complex heterogeneous tissues, such as liver and kidney tissues, will be fabricated successfully.⁹ This will open the door to making viable live implants, as well as printed tissue and organ models for use in drug discovery.⁹ It may also be possible to print out a patient's tissue as a strip that can be used in tests to determine what medication will be most effective.¹ In the future, it could even be possible to take stem cells from a child's baby teeth for lifelong use as a tool kit for growing and developing replacement tissues and organs.³

In situ printing, in which implants or living organs are printed in the human body during operations, is another anticipated future trend.¹³ Through use of 3D bioprinting, cells, growth factors, and biomaterial scaffolding can be deposited to repair lesions of various types and thicknesses with precise digital control.¹⁰ *In situ* bioprinting for repairing external organs, such as skin, has already taken place.¹³ In one case, a 3D printer was used to fill a skin lesion with keratinocytes and fibroblasts, in stratified zones throughout the wound bed.¹³ This approach could possibly advance to use for *in situ* repair of partially damaged, diseased, or malfunctioning internal organs.¹³ A handheld 3D printer for use *in situ* for direct tissue repair is an anticipated innovation in this area.¹⁰ Advancements in robotic

bioprinters and robot-assisted surgery may also be integral to the evolution of this technology.¹³

CONCLUSION

3D printing has become a useful and potentially transformative tool in a number of different fields, including medicine.⁶ As printer performance, resolution, and available materials have increased, so have the applications.⁶ Researchers continue to improve existing medical applications that use 3D printing technology and to explore new ones.⁶ The medical advances that have been made using 3D printing are already significant and exciting, but some of the more revolutionary applications, such as organ printing, will need time to evolve.³

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