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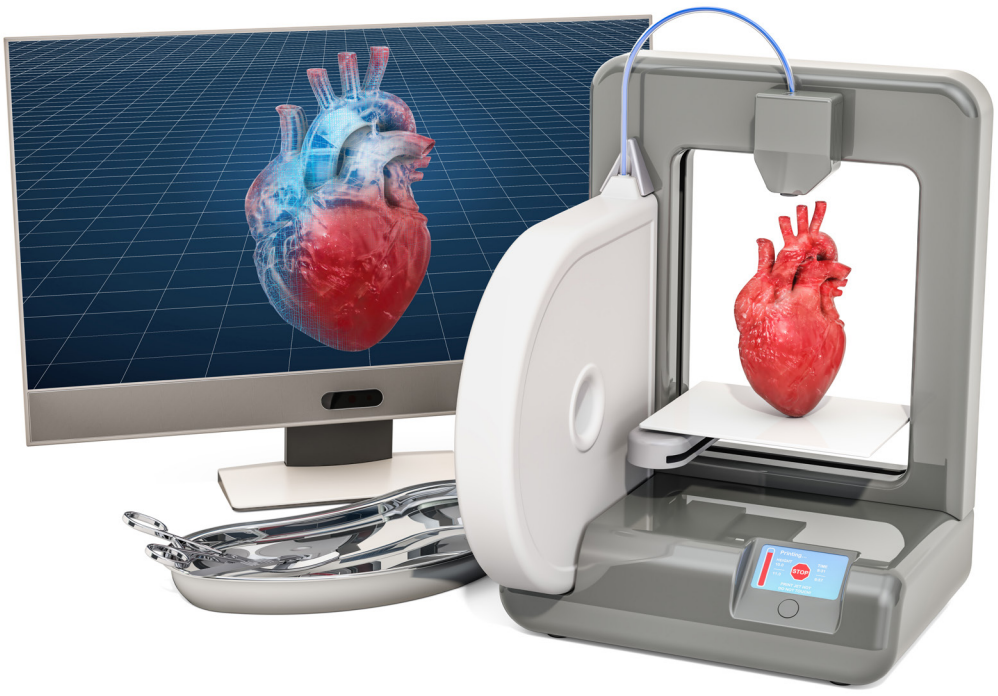
# An Overview of Clinical Applications of 3-D Printing and Bioprinting



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## Background

In the 1980s, the first 3-D printing (3-DP) patent was filed by Charles Hull.[1] Since then, substantial hype and growing demand has developed around a technology class that some anticipate will fundamentally change manufacturing across industries.[2-5] Promising medical solutions such as bionic limbs, replacement organs, and advanced pharmaceutical delivery systems have been conceived, yet technical, scientific, and regulatory challenges persist. While some medical applications of 3-DP are diffusing into practice, many remain in the exploratory research and development phase.[6] This bulletin provides an overview of clinical applications of 3-DP and bioprinting, including the current context in Canada and other countries, emerging technology developments, potential implementation issues, and challenges for the assessment and evaluation of 3-DP technologies.

### What is 3-D Printing?

Additive manufacturing or 3-DP is the process by which 3-D objects are created, layer by layer, from raw materials guided by a digital file.[7-10] Although there is some disagreement in 3-DP terminology,[11] generally, additive manufacturing describes large-scale, industrial-grade printers used to print at a commercial scale, whereas 3-DP describes smaller printing, using consumer-grade printers (e.g., for rapid prototyping or models).[7] This bulletin uses the term 3-DP to describe both approaches.

In health care, there is great interest in 3-DP as a tool that may help clinicians, health care administrators, and device manufacturers to: [12-16]

- visualize and plan complex interventions
- create personalized or patient-specific devices
- build devices of complex internal and external shape and structure from biocompatible materials
- produce devices or supplies on-site, as needed
- streamline supply chains
- reduce inventory needs
- reduce labour costs.

3-DP may also appeal to health care providers who regularly use small parts suitable for printing (e.g., dental crowns)[15] and promises to help move health care from its current one-size-fits-all approach to small-batch or even patient-specific medical devices.[16]

3-DP is an active area of research with many studies underway. At the time of the grey literature search for this bulletin, more than 100 clinical trials of clinical applications of 3-DP were registered as in progress or recruiting in the International Clinical Trials Registry Platform[17] and ClinicalTrials.gov,[18] and 14 systematic reviews of 3-DP applications in health care were registered in PROSPERO.[19]

### What is Bioprinting?

Part of a complex process known as biofabrication, bioprinting is a 3-DP technique that combines living cells (e.g., stem cells) and supportive biomaterials (e.g., scaffolds on which cells can grow) into so-called bioinks.[13,20,21] These bioinks are printed into pre-specified computer-generated designs with the goal of eventually maturing into specific tissues.[13,20,21]

Driven in part by a lack of donor tissues and organs,[22] advances in "bioprinting instrument capabilities; printing speed and precision; better preservation of living cells pre- and post-printing; printing multiple bioinks together; and innovations in bioink and support material formulations allowing printing of soft flexible tissue materials"[23] are helping the progress of research and development in the field.

While in vivo work in regenerative medicine is still in the very early stages of research — with full organ transplant seen as the long-term goal[23] — a number of companies around the world are actively working to improve bioprinting by expanding the types of materials and optimizing technological approaches.[24]

### Scope

In 2016, CADTH produced a brief horizon scan on 3-DP applications in health care.[25] This bulletin expands on this work, focusing primarily on the clinical applications of 3-D printing and bioprinting. Other health care applications of 3-D printing and bioprinting, including 3-DP of pharmaceuticals, are also discussed.

## Methods

CADTH Horizon Scanning bulletins are not systematic reviews and do not involve critical appraisal or include a detailed summary of study findings. Rather, they present an overview of the technology and available evidence. They are not intended to provide recommendations for or against a particular technology.

### Literature Search Strategy

A series of limited literature searches were conducted using the following bibliographic databases: MEDLINE, Embase, and the Cochrane Library. Grey literature was identified by searching relevant sections of the *Grey Matters* checklist (cadth.ca/grey-matters). The searches were completed on October 2018 and limited to English-language documents published after January 1, 2008. Regular alerts updated the search until project completion. Conference abstracts were excluded from the search results.

### Study Selection

One author screened the literature search results and reviewed the full text of all potentially relevant studies. Studies were considered for inclusion if the intervention was a clinical application of 3-D printing or bioprinting. The final selection focused primarily on existing evidence syntheses including systematic reviews and meta-analyses. Studies providing direct cost data, narrative reviews, and expert commentaries were also included. Grey literature was included when it provided additional information not available in the published studies selected.

### Peer Review

A draft version of this bulletin was peer-reviewed by a clinical expert.

### Stakeholder Review

A draft version of this bulletin was posted publicly for stakeholder review.

## The Technology

3-DP objects and bioprinted objects can be created using a number of different production techniques that, in general, share the following common components:[7,14,26]

- data (e.g., images) for the design software to use
- computer software for modelling, designing, and translating digital models into printer instructions
- a computer-controlled printer
- appropriate layering materials for producing the desired object.

Common production techniques for 3-DP and bioprinting used in clinical applications are described in Table 1.

Regardless of the technique used for printing, the production of 3-DP objects (including medical devices) involves three general steps: pre-processing, printing, and post-processing.[7,26,33] Bioprinting follows a similar production path but with some notable differences throughout the process.[21,23] These production steps (with additional considerations for bioprinting) are described in more detail in Table 2.

Other factors that may also be taken into consideration when producing a 3-DP object include:

- material selection, which depends on both the needs of the object being printed and the requirements of the printing process and equipment being used[26]
- design considerations beyond the object itself, such as the support structures and the thickness of layered materials.[26,33]

While the aforementioned production steps describe a typical approach to building a 3-DP object itself, manufacturers can use 3-DP to build "negative" structures for use as casts or molds.[13]

## Emergence of 3-D Printing and Bioprinting in Canada

A 2017 report from Canada's Standing Senate Committee on Social Affairs, Science and Technology identified 3-DP as one of three areas anticipated to present challenges to the Canadian health care system.[34] Presentations from Health Canada to the committee indicated that devices produced using 3-DP have already been approved for use in Canada.[34]

Our search of the grey literature identified many examples of research, development, and production in 3-DP for health in Canada.[35-45] Examples of Canadian activities include hospital scale printing,[40,46,47] academic initiatives and collaborations,[37-39,44,48] not-for-profit initiatives,[35,49] and for-profit start-ups and

## Table 1: Description of Common Production Techniques for 3-D Printing and Bioprinting

| 3-DP Techniquesa | Description and Considerations[7,21,26-31] |
|---|---|
| **Vat Photopolymerization** | |
| **Stereolithography (SLA)**[27,28 a] | The oldest method of 3-DP. Uses a scanning laser to scan a reservoir of photosensitive liquid polymer (resin), selectively solidifying layers from the surface of the liquid based on the design data. As layers are hardened, a movable build platform descends to increase the depth of the material. The process uses software-generated supports, which have to be removed from the finished product. |
| **Powder-Bed Fusion** | |
| **Selective laser sintering (SLS)**[28] | Uses a laser or electron beam to trace a 2-D slice in a bed of fine thermoplastic powder composed of a variety of materials (e.g., nylon, metals), heating the powder to the point that it fuses together. Once the 2-D slice is traced, a new layer of powder is added to repeat the process until the object is formed. Referred to as direct metal laser sintering when the process is applied to metal alloys. |
| **Selective laser melting (SLM)**[29] | Similar to SLS, but the powder is heated by the laser to the point that it fully melts, creating a homogenous part. It may be used if you are only using a single metal powder. The material is stronger but the porosity cannot be controlled. |
| **Selective heat sintering (SHS)**[32] | Similar to SLS but uses a thermal print head as opposed to a laser to sinter the powder. It allows the printer to be smaller in size. |
| **Material Extrusion** | |
| **Fused filament fabrication (FFF)**[28b] | Forms an object using a computer-controlled extrusion nozzle to deposit layers of heat-softened polymer melted from a filament. |
| **Material Jetting** | |
| **Polyjet**[30] | Uses inkjet technology to deposit photopolymer with an inkjet head that moves in the x- and y-axes. Each layer is cured, and successive layers are printed over top and fused. Products have high resolution but may be weaker than other techniques. |
| **Bioprinting Techniques** | **Description and Considerations**[7,21,26-31] |
| **Extrusion-based**[21] | Uses a robotic system to continuously extrude bioinks in one long filament onto a scaffold. Forces created by the extrusion may impede cell survival, but the resulting structures are more mechanically robust than other methods. |
| **Droplet-based**[21] | Bioinks are placed, drop-by-drop, into precise positions, using a variety of techniques to form a 3-D shape. Cells have good viability and the technique is relatively rapid and with high resolution. Limitations include the potential for variation in droplet size and clogging of the nozzle. |
| **Laser-based**[21,31] | Uses laser energy absorption to propel cell hydrogel droplets onto a surface. Compared with other methods, it has good cell viability and minimal clogging but is more expensive and time-consuming to do it in high resolution. |

2-D = two-dimensional; 3-D = three dimensional; 3-DP = 3-dimensional printing.

[a] This is not a comprehensive list of 3-D printing technologies; rather, some examples of approaches used in clinical applications.

[b] Also referred to as fused deposition modelling (FDM).

## Table 2: A General Approach to the Production of 3-D Printed Objects and Considerations for Bioprinting

| Production Step | 3-D Printing | Bioprinting Considerations |
|---|---|---|
| **Pre-processing** | • Acquire images (e.g., from MRI or CT).[7,33]<br>• Convert images into files the printer can use (e.g., computer-aided design filesa or additive manufacturing files).[26,33]<br>• Select design inputs (e.g., "surface characteristics, object rigidity…reaction to external forces applied during use").[26] | • May include:<br>◦ collection of tissue samples (for a source of autologous cells)<br>◦ work with stem cell lines<br>◦ developing processes for biomimicry (to allow for cell growth)[21] |
| **Printing** | • Select the layering material(s)[7,26] (e.g., metal, plastic, ceramic, glass, liquid, and living cells [used for bioprinting]).<br>• Select an approach to printing.[7,26-28]<br>• Select the software to prepare design files for printing.[26] | • Printing materials are bioinks:[21,23] a mixture of cells, growth matrix, and nutrients loaded into printing cartridges.[23]<br>• Certain methods can impede cellular growth and should be considered when selecting a bioprinting method.[21,23]<br>• The speed of printing is also important because cells cannot survive outside an incubator for long.[23]<br>• Cell material needs to interact and printing at a high resolution can facilitate this.[21] |
| **Post-processing** | • Remove any remaining support structures and residues.[26]<br>• Final quality assurance testing.[26] | • This is focused on continued growth and development of the cells.[21]<br>• Structures must be loaded into an incubator and provided with appropriate biological conditions to grow into mature tissue.[23] |

CT = computed tomography; MRI = magnetic resonance imaging.

[a] Note: Design files can also be informed using lessons learned from previous product design.[16]

organizations.[36,41-43,45,50-52] A network of private, public, academic, and not-for-profit organizations, Canada Makes — "dedicated to promoting the adoption and development of advanced and additive manufacturing (AM) in Canada" — includes a section dedicated to 3-DP in medicine and dentistry on its website.[53]

## Regulatory Considerations

As emerging and potentially disruptive health technologies, 3-DP and bioprinting present challenges to existing regulatory frameworks. Decisions around these frameworks could affect the adoption of 3-DP within the health system.[54] This section discusses approaches to 3-DP and bioprinting in Canada and around the world.

### *Canada*

In Canada, medical devices produced using 3-DP are subject to the Medical Devices Regulations.[55] In August 2018, Health Canada announced it was beginning to develop guidance for manufacturers wishing to obtain licences for 3-DP medical devices.[54] A draft guidance document was released for comment in October 2018 and final guidance is expected in the spring of 2019.[55] Feedback on the guidance issued has been posted publicly by some stakeholder groups.[56] The guidance is intended for manufacturers (including hospitals producing 3-DP devices for distribution outside their organizations) of 3-DP Class III and Class IV implantable medical devices and is supplementary to existing evidence requirements for all Class III and Class IV devices.[55] It does "not provide guidance on third-party software, custom-made devices, patient-specific

anatomical models, devices manufactured at point-of-care, and devices with biological components."[55] The draft guidance is considered a first step for 3-DP policy in Canada and is intended to evolve, along with the technology.[55]

Health Canada's draft guidance notes that the production of 3-DP devices presents some unique considerations for manufacturers and that, in addition to the data required for the approval of all Class III and Class IV medical devices, additional information may be required for the approval of 3-DP medical devices.[55] For example:

- Manufacturers should specify the starting materials, any additives, and the 3-DP technique used for production.
- Manufacturers should indicate if all or part of the device is 3-D printed.
- Submissions should include a design philosophy explaining why 3-DP was the appropriate manufacturing approach.
- Records of printer maintenance and cleaning, validation of consistent performance, the accuracy of reproduction of patient-specific images, and the validation of printer-material combinations should be retained.
- The processes for removal and possible reuse or recycling of layering materials should be validated.
- Verification and validation of the software for design and printing is required.
- Biocompatibility testing should be conducted on finished devices.
- Processes for the post-processing removal of residues, and excess layering material and sterilization of 3-DP devices, should demonstrate that the bioburden is minimized and consider how sterilization may affect the final product.

### *United States*

In recognition of the wide range of 3-DP applications, the FDA regulates technologies as either medical devices, biologics, or drugs.[9] As of December 2017, more than one hundred 3-DP devices currently on the market had been reviewed by the FDA.[57]

Initial FDA guidance for 3-DP medical devices was issued in 2017, acknowledging the unique design, manufacturing, and device testing requirements.[10] Bioprinting is not included in this guidance.[10] The document covers technical considerations for quality systems based on regulatory classification and associated regulation to which the device is subject, as well as manufacturing considerations, and the information required for regulatory notifications, and submissions.[10] It is meant to supplement, not replace, other applicable regulatory guidance for medical devices.[10] The FDA noted that this guidance would evolve as understanding develops on factors such as non-traditional manufacturing sites and supply chains, the use of biological printing material,[20] and point-of-care device considerations.

The FDA also conducts primary research on 3-D printing at several sites to help understand its impact on the safety and quality of medical technologies.[10] Findings from this research aim to inform policy development and guidance updates.[10] Support for innovation and access is offered through the Emerging Technology Program,[58] which allows early engagement with manufacturers hoping to bring their 3-DP technologies to market.[10]

### *Europe*

In Europe, the regulation of 3-DP health technologies is complex and is governed, as of 2017, by three frameworks: the European Medical Devices Directive, the Invitro Diagnostic Medical Devices Directive, and the Active Implantable Medical Devices Directive.[14] Regulation is dependent on the type of device being printed (i.e., patient-specific, customizable, or mass produced).[14] Consideration must also be made for the printer, software, and materials used.[14] Hospital-made devices are exempt from some regulations provided that no equivalent product exists, the hospital is not mass-producing items, and quality manufacturing standards are maintained.[14]

### *Australia*

In Australia, consultations are underway on proposed changes to the regulation of medical devices to better address the introduction of personalized medical devices, including 3-DP devices.[59] The proposed changes include:

- adopting international definitions (e.g., custom-made, patient-matched) developed by the International Medical Device Regulators Forum (IMDRF)[60]
- creating a framework to allow clinicians to produce low-risk devices without manufacturing certification
- regulating anatomic models in a way similar to diagnostic images
- regulating "medical devices with a human origin component" (e.g., bioprinted patient-specific implants) as medical devices and not as biologics.[59]

### Lack of Fit-for-Purpose Regulatory Frameworks for Bioprinting

Bioprinting does not fit within existing regulatory frameworks or guidance.[20] It spans several areas of health care — including but not limited to regenerative medicine, medical devices, and biologic drugs — making it difficult to apply existing systems.[20] The customized single-patient-use nature of bioprinted interventions suggests the potential for exemption from, or the ability to circumvent, regulatory processes.[20]

The exclusion of bioprinting from existing 3-DP guidance and the lack of a dedicated regulatory framework pose challenges in understanding the applicability of current regulatory requirements and addressing the uncertainty of harms.[20,61,62] Many countries have noted challenges in trying to develop a dedicated framework.[20] It is unclear whether bioprinted interventions will receive balanced consideration of their efficacy and safety without the presence of a tailored regulatory process.[20]

### Other Considerations

Our literature search identified a number of other possible questions and considerations for the regulation of 3-DP medical devices; for example:

- What are the biocompatibility needs for materials used for 3-DP medical instruments (e.g., surgical guides)? If 3-DP medical instruments have less biocompatibility requirements than 3-DP implantable devices, does this open up the possibility of using different products and materials?[13]
- A 2016 systematic review of surgical applications of 3-DP noted that, for hospitals wishing to produce their own devices and equipment, regulatory requirements are a concern and might prevent 3-DP from being adopted.[63]
- If there are requirements to label and be able to track medical devices, how does this work for custom 3-DP devices?[14]

## Who Might Benefit?

It has been suggested that 3-DP will bring advantages to many aspects of health care such as diagnostics (using medical imaging to create models that aid in visualization), surgical planning, and personalized medicine.[7] Applications of bioprinting may disrupt existing models of organ and tissue donation, although these applications are likely further in the future than other 3-DP applications.[7] Many clinical areas are currently using, or investigating the use of, 3-DP. Because of this, 3-DP has the potential to affect Canadians living with many different health conditions.

## Clinical Applications of 3-D Printing

Initially reserved for complex cases, 3-DP is becoming more common or routine in some clinical areas.[64] A 2018 narrative review of registered clinical trials found orthopedics, dentistry, and maxillofacial surgery to be the most active areas of ongoing research.[65]

3-DP health care applications are generally categorized in the literature into the following applications:[8,13,14,26,28,66,67]

- anatomical models (e.g., for surgical preparation, planning, or to aid diagnosis)
- surgical guides
- tools and instruments
- implants and therapeutic devices
- prosthetics
- tissues and organs
- dental applications.

3-DP medical devices can be further classified into three types, based on their degree of customization:[14]

- custom-made medical devices (i.e., devices unique to an individual)
- customizable medical devices (i.e., mass produced using a standard process and individualized to specific patients)
- standard medical devices (i.e., mass produced using 3-DP because of device complexity or to lower costs).

Information on applications of 3-DP in dentistry; prosthetics, orthotics, and assistive devices; and surgery are summarized. Because of overlap between clinical specialties (e.g., oral surgery and dentistry), some applications are discussed in more than one section of this report.

### Dentistry

Advances in dental imaging (such as cone beam computed tomography [CT]) have resulted in increased interest in 3-DP for dentistry.[68] 3-DP applications in dentistry include :

- orthodontics[7,69] (for making and positioning brackets, as well as aligners)
- dental crowns and partial dentures[27,70]
- removable complete dentures[70,71]
- oral surgery:[69]
  - surgical guides placed over teeth to align drills[27,68]
  - access guides for root canals[68]
  - replica teeth to prepare autotransplantation sites[68]
  - dental implants.[69]

## Prosthetics, Orthotics, and Assistive Devices

The use of 3-DP in both prosthetics (devices that replace missing body parts) and orthotics (the design of external devices that modify the structure and function of the body) may be beneficial because of:[13,64,72]

- customization to offer a better fit and ability to adjust or increase device functionality
- lighter weight
- lower costs to make the devices available to a broader market.

These potential benefits are of particular interest for children who can quickly outgrow expensive devices.[64]

Other examples include using 3-DP to produce customized ear shells (devices that connect hearing instruments to a person's ear canal) for hearing aids;[15] and the printing of assistive devices, such as straw holders and key turners in occupational therapy.[73]

## Surgery

In surgery, 3-DP may provide surgeons with a better understanding of complex anatomy when planning surgeries, allow for customized or patient-specific implants and surgical guides, and ultimately reduce operating room time.[63,74] Advantages may include shorter operative time and reduced costs, while disadvantages to 3-DP may include reactions to the material used and added planning time.Surgical applications of 3-DP have been grouped into the following categories:[28]

- anatomic models[67] (for preoperative planning)
- surgical instruments
- implants and prostheses, splints and external fixators.[67]

Imaging in surgical applications of 3-DP is conducted using CT and magnetic resonance imaging (MRI). As well, "a number of other 3D imaging options have been used in 3D printing, such as: cone beam CT, CTA [CT angiography], MRA [magnetic resonance angiography], PET [positron emission tomography], MRCP [magnetic resonance cholangiopancreatography], 3D echocardiography, 3D laser scanning systems, and even images captured on an iPhone."[67]

Areas of research in surgical applications include surgical guides, models for surgical planning, or custom implants.[74] Areas in development within surgical applications include orthopedics (particularly knee surgery), maxillofacial surgery (cranial and spinal surgery), dental surgery, cardiovascular surgery, cerebrovascular surgery, otolaryngology, and general surgery.[74]

Examples of surgical applications of 3-DP are discussed, by subspecialty, in the following sections.

### *Neurosurgery*

In neurosurgery, advances in imaging have been beneficial to patient care by allowing clinicians to observe small and intricate structures inside the nervous system.[75] 3-DP offers the potential of improved visualization of the relationship between complex structures when planning a procedure.[75] Because the spine has complex anatomy and is surrounded by delicate structures, 3-DP models and devices that help surgeons plan and accurately execute procedures could also help improve patient outcomes.[76] It has been reported that, as case complexity increased, so did the benefits of using 3-DP such as reduced operative time and perioperative blood loss. 3-DP surgical guides were reported to help mitigate the risks of procedures.[76]

The use of 3-DP in neurosurgery[75] includes the development of patient-specific anatomical models, the design of devices to assess and treat neurosurgical conditions, and biological tissue-engineered implants. In addition, subspecialty 3-D printing applications in neurosurgery are listed in Table 3.[75,76]

## Orthopedics

Applications for 3-DP in orthopedics include using anatomical models to visualize and plan for fracture repairs,[22,77] create implants for arthroplasty,[22] prepare contour plates and surgical guides,[64] and create lightweight, custom casts.[22] Visualizing tibial plateau fractures can be difficult; it has been reported that 3-DP

## Table 3: Subspecialty Applications of 3-DP in Neurosurgery[75]

| Subspecialty | Application | Example |
|---|---|---|
| **Cerebrovascular**[75] | Surgical planning and modelling | Cerebral aneurysm surgery |
| **Neuro-oncology**[75] | Surgical planning and modelling | Visualization of the relationship between skull, tissue, and tumour for resection — including incorporating information from fMRI |
| | Neurosurgical devices | Proton range compensator — creates a conformal dose distribution to protect tissues surrounding the tumour |
| **Functional**[75] | Surgical planning and modelling | Placement of intracranial electrodes for treatment-resistant epilepsy |
| | Neurosurgical devices | Patient-specific head casts to reduce movement when monitoring brain activity |
| **Spinal**[75,76] | Neurosurgical devices[75,76] | Patient-specific screw guides for optimizing the trajectory of pedicle screws used for spinal fixation |
| | Custom implants | Used in complex cases (e.g., for congenital malformations or the replacement of whole vertebrae), where an individualized approach is important for the prognosis |
| | Mass-produced implants[76] | Devices with improved geometry and control of porosity and roughness for better osteointegration |
| | Biological implants[75] | Early research into implants to replace intervertebral disks instead of spinal fusion |
| | Surgical planning and modelling[76] | Used to provide a more complete understanding of the pathology and to simulate the procedures |

3-DP = three dimensional printing; fMRI = functional magnetic resonance imaging.

could help overcome preoperative planning challenges related to visualizing the injury. Outcomes reported included operating time, intraoperative blood loss, time to bone union, follow-up functional outcomes, and complications.[77]

3-DP has also been used in limb and pelvic injuries to help repair damage to many bones of both the upper and lower extremities, including those of the hands and feet.[64]

## Vascular and Endovascular Surgery

In vascular and endovascular surgery, 3-DP applications focus on the visualization of anatomical structures.

3-DP models have been developed for infrarenal and juxtarenal arteries, abdominal aortic aneurysm, and thoracic aorta pathology and 3-DP of vessel pathologies have been used to better understand anatomy and post-surgical complications.[78]

## Plastic and Reconstructive Surgery

3-DP is being studied and used in plastic and reconstructive surgery for procedural planning, the creation of surgical tools, and the customization of implants.

3-DP has been studied or used in maxillofacial surgery, dental implant surgery, mandibular reconstruction, orthognathic surgery, and midface reconstruction.[79] Common applications include anatomic models, surgical guides (most common application), occlusal splints, patient-specific implants, and facial epithesis.[79,80]

The increased availability of affordable 3-D scanning technology may improve the ability of clinicians to make highly patient-specific products, which can be important in plastic and reconstructive surgery applications.[81] Applications reported included surgical planning; upper limb and hand prosthetics; facial reconstruction; breast reconstruction; ear, nose, and cartilage reconstruction; and skin grafting.[81] It has also been used in skull reconstruction, repairing orbital fractures, and in orthognathic procedures. [82]

## Hepatobiliary Surgery

Applications of 3-DP in hepatobiliary surgery include models for surgical planning for liver surgery, including as a supplement to medical imaging. The clinical value and application of 3-DP in liver surgery may be in printing models to plan for surgery.[83] It has been reported that printing time varies from 11 hours to 100 hours, and that some models take weeks to be printed and delivered.[83]

The production of models can be used as an adjunct or alternative to imaging because of the complex, unique anatomy involved in procedures such as liver transplant or cancer resection.[84]

### Urology and Renal Surgery

In urology and renal surgery, 3-DP models are used for visualization to assist diagnosis; and in structural visualization to plan for surgery, transplantation, and other procedures.

In renal surgery, 3-DP is used to visualize renal tumours for removal.[85]

In urology surgery, 3-DP applications include pre-surgical planning to remove renal masses, building molds to visualize the renal collection system for patients with kidney stones (to facilitate novel treatments), and producing models of a donor's kidney and pelvic cavity to plan a kidney transplant.[86] For prostate conditions, 3-DP models have been used alongside MRI to diagnose prostate cancers, to help plan prostate surgery, and to plan complex urologic surgeries.[86]

In urologic cancer, 3-DP has been applied to generate anatomical models for planning and surgical simulation.[87]

### Cardiac Surgery

Surgical planning is noted as a potential application of 3-DP in cardiac surgery. The use of 3-DP heart models for surgical planning for people with congenital heart defects has been reported.[88]

### Anesthesiology

3-DP has been used to produce anatomical models to preoperatively size airway devices and plan for airway management.[89] Bioabsorbable airway splints have also been produced using 3-DP.[89]

## Clinical Applications of Bioprinting

The development in the field of bioprinting is being driven largely by "[the medical needs of] aging populations; increasing unmet demand for organ donors; trends towards non-animal testing on therapeutics using 3-D cell culture platforms; clinical needs in wound care; and joint repair and replacement surgeries."[23]

Bioprinting is being explored for the purposes of repair, replacement, or regeneration to develop an assortment of tissues including cartilage, bone, skin and periodontal tissues; other vascularized tissues; and cardiovascular tissues.[13,90,91] Bioprinted tissues are being investigated as analogues for toxicity testing, disease modelling, and for patient-specific drug screening, with the potential to eliminate testing on animals.[13]

Bioprinting applications noted the following areas of inquiry in descending order of most to least developed and validated:[23]

- tissue modelling (drug discovery and development)
- toxicology testing (drug screening and cosmetics)
- engineered tissues (regenerative medicine, prosthetics, and dental applications)
- transplantation (full or partial organs as part of regenerative medicine).

## Other Health-Related Applications of 3-D Printing and Bioprinting

### 3-D Printed Medications

The potential benefits of using 3-DP techniques for producing medications include the ability to personalize a medication dose, combine the delivery of medications, and avoid the use of bulking agents or fillers that a person may be intolerant to (such as lactose).[16]

One example is levetiracetam (a treatment for epilepsy), approved by FDA in 2015.[7] This product is produced using a 3-DP technique called ZipDose that combines power and liquid printing to produce high-dose, quick-dissolving pills.[92]

A structured review of 3-DP of medications was published in 2013.[93]

### Clinician Education and Training

Examples of using 3-DP models to educate and train clinicians are common in the literature. Clinical areas where 3-DP training and education models are in use include pathology, urology, neurosurgery, vascular and endovascular surgery, congenital heart disease, and anesthesia.[67,75,78,86-89,94]

In vascular and endovascular surgery, the use of 3-D printing has been discussed regarding the potential of moving from a traditional learning model of "see-one, do-one, teach one" to an approach that includes simulation using 3-DP models.[78]

3-DP could also be used to build a library of pathologies for future education.[28] However, the utility of practising on such models, particularly those made from a single material, might not accurately replicate the feel of actual human tissues.[28] Advances in 3-DP now allow for models to include different tissue types, which may be more realistic as teaching models.[94]

While experienced clinicians may be able to clearly visualize internal structures, it is possible they could benefit from training using 3-DP anatomical models when preparing for complex interventions.[13]

### Patient Education

Using 3-DP models may help patients understand their condition (e.g., visualizing anatomy in congenital heart disease[88]), understand complex anatomy and procedures (e.g., during the preparation for vascular surgery[78] or liver cancer resections[87]), and improve shared understanding when seeking informed consent.[28,82]

### Other Applications

3-DP is also used to produce phantoms — objects that are specially designed to be scanned or imaged — for testing imaging systems.[95]

## Implementation Issues

The integration of 3-DP into routine clinical practice goes beyond the effectiveness and safety of individual technologies. There are several potential implementation considerations related to technical features, cost, legal and ethical issues, and patient-related factors.

### Technical Considerations

There are a range of important considerations in the implementation of 3-DP related to factors such as the technological and manufacturing process, the materials used, and technical limitations of the technology.

3-DP requires a minimum level of image and resolution quality.[26,82] Successful printing, which is especially challenging in specialized fields such as vascular surgery, can be highly dependent on the quality of imaging and printers available.[78] There are also many software options available and care is needed to ensure errors do not occur when converting data from one file type to another.[26] For 3-DP in craniofacial plastic surgery, it has been noted that the need for software specifically designed for these clinical applications was a barrier to uptake in the field.[82] Issues with accuracy (poor image resolution) and artifacts (related to CT being unable to scan metal) were also noted.[82]

Uncertainty about the materials used for 3-DP has also been raised. For example, a review of prosthodontic applications of 3-DP noted that more research into the mechanical properties of materials used and the final products themselves was necessary.[70] Concern has also been expressed about the limited availability of 3-DP compatible materials, which could limit the potential for its use in health care.[13] That is, common biocompatible materials are often unsuitable for 3-DP and common materials used in 3-DP are often not biocompatible.[13] Another issue raised is a need for a better understanding of what material microarchitectures, or internal structures, result in the best performance.[13] It has been noted that 3-DP cannot replicate all surgically useful information (such as joint instability) and, unlike some types of imaging, cannot provide real-time information.[76]

In a report about 3-DP use in maxillofacial surgery, it was noted that although low-cost printers are available, 3-DP was more frequently being outsourced to a commercial medical devices manufacturer as opposed to being printed in-house.[79] Less complex printing for items such as anatomical models may be more suitable for in-house 3-DP.[79] In the case of self-printing, patients may not receive the support needed to maximize the safety and utility of such a device.[72]

### Cost and Administration

#### *3-D Printing*

The literature search aimed to identify cost-related information about 3-DP in health care. Few studies were identified that directly evaluated costs; however, many studies and reports discuss them indirectly.

Typical costs of 3-DP include the printer, software, high-resolution computer screens, high-powered computers, a high bandwidth computer network, printing materials, post-processing equipment, facility costs and upgrades (i.e., fume hoods, ventilation set-up), staff training, equipment maintenance contracts, and personnel salaries.[67,96] Costs also depend on the type of manufacturing (i.e., consumer versus commercial).[74] A 2018 systematic review of 3-DP in liver surgery noted that only a portion of included studies discussed costs and that what was reported was dependent on

the technique and materials used.[84] One pilot study of 3-DP in maxillofacial surgery considered procedural costs and associated variables such as operative time and surgical complications.[97]

A 2018 KCE (Belgium) report found there was not much information available on the cost-effectiveness of incorporating 3-DP into clinical practice and noted no studies were found that reported on cost utility.[14] Similarly, a 2016 systematic review of studies on 3-DP applications in surgery noted that only about 10% of included studies discussed cost-effectiveness.[74] However, the authors found mixed reporting about the costs of using 3-DP, with some reporting higher costs and some reporting lower costs associated with the use of the technology.[74]

While cost was identified as a barrier to 3-DP in many included studies, in a 2016 systematic review of surgical 3-DP, the authors noted that cost is a concern when introducing any new health technology.[63] The value of 3-DP may also be difficult to assess. For example, while the time required for the 3-DP process may greatly exceed the time saved in the operating room by using a 3-DP model or device, the cumulative savings in operating room costs are likely greater than the additional expense required to produce 3-D printed tools.[63] It may also be difficult to generalize costs across institutions because of different practices.[63] 3-DP may also allow for inexpensive production throughout the life of a device — with the first device costing a similar amount to the last, something that is uncommon with other forms of manufacturing where prototype models may involve substantial costs.[81]

A number of articles identified reported direct cost information and considerations. These examples are summarized in Table 4.

Moving away from costs, a 2017 systematic review of 3-DP in liver surgery noted that 3-D modelling use is not widespread because of a lack of technicians with specialist knowledge in interpreting medical imaging.[84] Specialized knowledge needed by both radiologists and technicians includes: "anatomical structure segmentation (automatic, semiautomatic, or manual), virtual modeling, preparation for 3D printing, the printing process itself, and post-processing."[84]

### *Bioprinting*

A 2018 review of the bioprinting process discusses affordability as a concern throughout production. The cost of bioinks depends on the materials used in their composition.[21] For example, as the concentration of cells increases, so does the overall cost of bioinks.[21] The high cost of current bioprinters may also be a barrier to the wider adoption of bioprinting in clinical use.[21] The processes required for successful bioprinting — for example, sterility — may also contribute to the expensive cost.[21] A 2018 review of bioprinting skin noted that costs included cells, scaffolds, and printers.[91] Other costs associated with bioprinting include post-processing (e.g., the need for bioreactors to grow the tissues).[21] Reported costs of bioprinters range from US$500 to US$200,000.[21]

## Legal Considerations

### *Data Ownership and Privacy*

3-DP (particularly for custom or patient-specific devices) requires individual patient data.[14] The method of data collection and use must be taken into account when considering 3-DP as part of a patient's care plan.[14] The use of computer-aided design files may lead to intellectual property disputes and privacy concerns,[98] and questions about a patient's right to access and own their own data.[14] It is not yet clear who will own the computer-aided designs, medical images, and final products, particularly when biological material is utilized.[98] To ensure patient data are kept private, 3-DP systems must also have adequate cybersecurity protocols in place.[26]

### *Liability*

3-DP deviates from standard chains of production, distribution, and use, making the question of who is the producer or manufacturer difficult to answer.[14] It is unclear whether responsibility for custom-designed implant failure could fall to, for example, the surgeon who designed the implant, the software engineer who built the design software, the printer manufacturer, the manufacturer of the materials used for the final product, or a combination of those involved in its creation.[14]

## Ethical Considerations

Some of the novel features of 3-DP are associated with ethical questions or considerations. For instance, the ability of 3-DP to augment structures and functions of the human body suggests potential exploitation of this feature for human enhancement (e.g., proactively replacing bones with 3-DP alternative materials for function and performance).[99] There is excitement and hope surrounding 3-DP, which may impact patient perceptions and expectations.[100] This must be weighed against the uncertainty regarding safety and efficacy, and the ethics of offering experimental treatments.[100]

## Table 4: Examples of Reported Costs of 3-DP Clinical Applications

| Clinical Specialty | Application | Reported Cost | Considerations |
|---|---|---|---|
| **Plastic surgery**[81] | Custom-printed implants | US$10,000 to US$15,000 | Noted outlier costs as low as US$30 |
| **Spinal surgery**[76] | Anatomic models | US$300 to more than US$1,000 | Cost of printing models would be in addition to standard surgical planning<br>The authors also reported time costs associated with the two to five hours required for printing but noted that these up-front costs to 3-DP may be offset by time savings in actual procedures |
| **Vascular and endovascular surgery** [78] | Anatomical models | US$4 to US$2,360 | N/A |
| | Printers | US$2,210 to US$50,000 | One high-end industrial printer had a reported cost of €230,000 |
| **Renal surgery**[85] | Anatomical models | US$100 to US$1,000 | Cost depended on materials used |
| **Congenital heart**[88] | Anatomical models | US$55 to US$810 | Cost depended on materials used |

3-DP = three dimensional printing; N/A = not applicable.

Another concern is the shift toward a decentralized manufacturing process.[101] Current safety regulations rely on centralized manufacturing processes and may not be sufficient if manufacturing occurs at point-of-care.[101] While some believe 3-DP may democratize access to personalized medicine, others believe complex 3-DP products — such as replacement organs, for example — may only be accessible by those with substantial resources.[99] This may depend on the funding and reimbursement structure, and the type of product or application.

### *Bioprinting*

Ethical considerations, specifically related to the introduction of bioprinting, have been summarized in a review by Gilbert et al.[20] The authors raise questions on several key topics including:[20]

- whether there should be restrictions on what (i.e., material and products) can be bioprinted
- the risks and challenges associated with testing bioprinted technologies in humans
- ethical questions about treatment irreversibility, loss of treatment opportunity, and treatment replicability
- the lack of guidance frameworks for the testing and regulation of bioprinting in humans.

Additional relevant ethical issues in bioprinting have been reviewed by others.[101,102]

### *Restrictions to Bioprinting Materials and Products*

Bioprinting has generated interest for its potential role in reducing disease burden and health care costs,[103] but there is also the potential for bioterrorism[104] and unauthorized use by those with access to printing equipment.[20] Gilbert et al. noted the conflicting desire to provide access to potentially lifesaving treatments while avoiding doing harm in the face of uncertainty.[20] Further, the risks may differ depending on the product being printed and the bioink used for its creation.[20] There may be ethical concerns with administering bioprinted treatments of animal or embryonic origin to those with religious or other ethical conflicts.[20] The potential for donor coercion to supply biological materials was also noted.[20] The authors also touched on the potential implications of the origin of the material and the possibility that certain materials may carry a higher risk of harm, such as disease transmission, than others. General ethical concerns with tissue engineering may also apply in the case of bioprinting.[20]

### *Risk of Testing Bioprinting in Humans*

In studying or testing bioprinted products in humans, Gilbert et al. noted that, because of the nature of the bioprinted interventions,

it is neither feasible nor ethical to conduct safety trials using the traditional approach of testing the intervention in multiple subjects.[20] For each new application, the patient would likely be acting as the "guinea pig" for their personalized and thus experimental treatment.[20] While it may be possible to standardize criteria and protocols, each treatment is unique and findings from one patient are not generalizable to the next.[20] Gilbert et al. suggested that adding therapeutic efficacy end points to earlier stage clinical trials, particularly when patients have life-threatening conditions, could increase the value of investigations in this context.[20] They also discussed the importance and challenge of obtaining transparent and comprehensive informed consent in an environment of substantial uncertainty, particularly given the hype and perception of lower risk when using autologous (whereby the patient is the donor) material.[20,105]

To help patients make informed decisions about 3-DP technologies, KCE Belgium recommended "giving the patient complete information on the existing alternatives and, as necessary, on the scientific uncertainty that the 3D-printed medical device concerned would be safer or more effective than the existing alternative."[14]

### *Irreversibility, Loss of Opportunity for Future Treatment, and Limited Replicability of Treatment*

Patients may not have the same opportunity to withdraw from a trial after the implantation of a bioprinted product.[20] Procedures may have limited reversibility, particularly when cells are inserted into an existing biological structure.[20] The inability to withdraw from a trial may limit the opportunity for access to future treatment, restricting patient autonomy.[20,106] Gilbert et al. (also citing others) raised the question of whether it is morally appropriate to implant bioprinted materials for safety testing given the uncertainty regarding the risk-benefit profile.[20,107-109] This is a concern given the current climate of extending experimental therapy opportunities in the regulatory context.[20] Further, treatment effects may not be replicable from patient to patient, as the intervention will elicit a genetically, structurally, and phenotypically unique response.[20]

## Considerations for Evaluation and Assessment of 3-D Printing and Bioprinting Technologies

Organizations conducting secondary research and evaluations of 3-DP technologies may encounter certain challenges and opportunities. Among these are the quality and maturity of the evidence, unique features of 3-DP that may warrant alternative study designs and data collection measures, challenges associated with the customized nature of the technology, and a lack of consensus on nomenclature.

Authors of literature reviewed for this bulletin often expressed concern with both the quality and quantity of available evidence (e.g., the lack of randomized controlled trials) for 3-DP in health, as well as a need for evaluation of relevant outcomes measures (e.g., the impact of 3-DP on surgical time and precision).[8,14,76,79,84,97,110,111]

The state of evidence may be a barrier to the adoption of 3-DP in health care.[65] Surgical fields such as maxillofacial surgery, orthopedics, and cardiology have been suggested to be more developed than other clinical applications.[65] A spike in registered 3-DP trials after 2015 has been reported, indicating the technology may be moving from a state of early ideas and research to one of more long-term study.[65] As noted earlier, bioprinting is less developed than 3-DP, with much of the existing body of literature focusing on in vitro experimentation and conceptual exploration.[21] In testimony to Canada's Standing Senate Committee on Social Affairs, Science and Technology, presenters commented that traditional randomized controlled trials may not be the most appropriate approach for assessing the safety and efficacy of innovative technologies like 3-DP and that alternatives should be considered.[34]

The current quantity and quality of evidence, and unique features of 3-DP, may present challenges in conducting comprehensive evaluations of the technology. Specific challenges may exist for conducting health technology assessments. In a project description and planning document for a health technology assessment on a 3-DP topic, EUnetHTA made note of several relevant considerations. These included but were not limited to inconsistency in regulatory and market access requirements, questions around the type of data collection needed to monitor long-term safety

outcomes, challenges identifying specific manufacturers and low manufacturer engagement, lack of standardization of the device due to customization, and the need for a technical expertise (in addition to clinical expertise) on the project.[112]

A 2017 review of taxonomy and terminology used in 3-DP research found that a wide range of terms are being used to describe these applications.[11] The authors noted that a consistent, common set of language is necessary for collaborative research and eventually for reimbursement of 3-DP technologies, and proposed that "3D Printing" be adopted as the common term.[11] The lack of consensus on terminology could present challenges when evaluating 3-DP technologies using epidemiological methods that rely on literature searching and review strategies, such as health technology assessments and systematic reviews.

## Final Remarks

Research on clinical applications of 3-DP and bioprinting has progressed, in both volume and stage of inquiry, with some applications exiting the exploratory phase and undergoing concrete clinical evaluation.[8,65] In parallel, there has been growth in Canadian and international initiatives in 3-DP.[35-45]

Hospitals and clinics stand to benefit from more rigorous research into the effectiveness and safety of 3-DP technologies.[8] Evidence could be made more robust through larger studies and greater consideration of the value of the technology.[14] Adopting a formal model, such as IDEAL (Idea, Development, Exploration, Assessment and Long-term study), as suggested by KCE Belgium, may help address issues in data collection and help pave the way for further implementation and reimbursement of 3-DP in health care.[14]

Concepts that could help foster research and development in bioprinting include open sourcing of hardware and software, open innovation (greater use of external ideas and technologies for internal business, and greater sharing of internal ideas with external businesses),[113] and developing a greater understanding of customer and market needs.[23]

Looking beyond the current state of 3-DP, 4-D printing — an approach that "adds a dimension of transformation over time, where printed products are sensitive to parameters like temperature, humidity, time etc." — may offer additional advantages in the medical field as smart implants, tools, and devices become more common.[114]

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