ACE OVERVIEW FOR NEW AND EMERGING HEALTH TECHNOLOGIES

3D Printing and Its Clinical Applications

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Summary of Key Points

- Three-dimensional (3D) printing is a type of additive manufacturing, a process of producing an object by joining raw materials, usually layer upon layer, guided by a digital 3D file based on medical images. It has the ability to create devices matched to a patient's anatomy or devices with very complex internal structures.
- 3D printing concerns multiple surgical domains, with many remaining in the exploratory research and development phase. It is most often used for i) surgical guides, from orthopaedics (guides for knee arthroplasties) to neurosurgery, spinal surgery, and maxillofacial surgery; ii) anatomical models for surgical planning in multiple disciplines or implant shaping in maxillofacial surgery; and iii) custom implants in cranial surgery and maxillofacial surgery.
- 3D printing is generally regulated under the same frameworks for medical devices. Recognising the challenges faced by the existing regulatory frameworks, some countries issued supplementary guidelines to cover design, verification and validation controls including the software used, manufacturing considerations and labelling. Note that hospitals manufacturing 3D-printed devices for use only on their own patients do not need to register the devices.
- Currently, few studies have rigorously assessed the effectiveness of clinical 3D-printed devices. The most reported benefits of 3D printing are reduced surgical time, improved clinical outcome (e.g., surgical precision), decreased risk of postoperative complications, or decreased radiation exposure. However, most of the claimed benefits are yet to be determined for most of its clinical applications.
- Given the current cost of 3D printing with large upfront costs, and the often limited or unproven benefits, it is questionable whether currently 3D printing would be cost effective for most patients and clinical applications.
- 3D printing of full-scale biological organs is still a long way from being a reality, however it has the potential to revolutionise medicine, making organ transplants and current synthetic artificial organs obsolete.
- There are several implementation considerations, relating to technical, regulatory, legal, financial and reimbursement aspects of 3D printing. Currently inconsistency in regulatory requirements, questions around the amount and type of data collection needed to monitor long-term safety and effectiveness, challenges in identifying specific manufacturers, lack of standardisation of the device due to customisation are some specific questions. Some other issues include:
    - Quality control of multiple production steps including digital processing to polishing of models to create realistic models;
    - Decentralised manufacturing process does not fit the current safety regulations which rely on centralised manufacturing processes and may not be sufficient if manufacturing occurs at point-of-care;
    - Unclear data ownership and privacy concerns, particularly for custom or patient-specific devices due to individual patient data, especially if hospitals outsource 3D printing to an external producer;
    - The quantity and quality of available evidence and unique features of 3D printing may present challenges in conducting comprehensive evaluations, particularly for health technology assessment.

I. Background

Three-dimensional (3D) printing is a type of additive manufacturing and the terms are often used interchangeably. It is a process of producing 3D object by joining raw materials, usually layer upon layer, guided by a digital 3D file.[1] This is different from subtractive manufacturing methodologies.

3D printing is not new and the first 3D printing patent was filed in the 1980s.[2] Since then, great interest has developed around it with some anticipating that it would fundamentally change manufacturing across many industries. However, technical (e.g. optimal process validation), scientific (e.g. assessment methods), and regulatory challenges persist, especially in the medical applications of 3D printing. While some medical applications are diffusing into practice, many remain in the exploratory research and development phase.[3] Despite this, the medical and dental sectors together account for about 13% usage of additive manufacturing, the third largest 3D printing market after the industrial and aerospace sector.[4]

During the 2019 July MTAC meeting, 3D printing was nominated as a potential topic for horizon scanning. Subsequently the topic was shortlisted for further elaboration due to its potential advantages especially in visualising and planning complex interventions and creating personalised devices. Further, 3D printing is also an active area of research with many studies underway. At the time of the literature search for this report, nearly 200 clinical trials of its applications were registered on ClinicalTrials.gov. In addition, scientific papers on the topic has increased sharply in recent years, with great innovations in the use of 3D printing appearing in the fields of maxillofacial, cardiothoracic and orthopaedic surgery.[5, 6] Due to its wide applications in various clinical specialities and a lack of specific scope during the nomination, it was decided that an overview be developed on the clinical applications of 3D printing to enable subsequent selection for further assessment.

This report provides an overview of clinical applications of 3D printing, including the regulatory status in different countries including Singapore, the potential benefits and implementation issues, and challenges for the evaluation of 3D printing technologies. Note that 3D printing in dentistry, medical training and patient education, and 3D printed medications are outside the scope of this report.

II. Technology

There are three typical steps involved in 3D printing process: pre-processing, printing and post-processing.[3] The details are summarised in Table 1. Various techniques and raw material, which is introduced into the machine as in an inkjet printer, are used for 3D printing. Generally, patient data and other relevant medical information are obtained to design the devices to be printed. This is done mainly by scans of the body part where the device will be implanted or of which a model will be made. The 2D images from the scan such as magnetic resonance image (MRI), computed tomography (CT) and ultrasound are then converted into 3D images and processed with the aid of special software – computer aided design (CAD). The lower part of the object is printed first and then a new layer is added on top of it, which keeps accumulating to gradually form the medical device.[4]

Table 1: General approach of 3D printed process[3]

Production step	Description
Pre-processing	• Acquire images (e.g., from MRI or CT). • Convert images into digital files the printer can use (e.g., computer-aided design files or additive manufacturing files). • Select design inputs (e.g., "surface characteristics, object rigidity…reaction to external forces applied during use").
Printing	• Select the layering material(s) (e.g., metal, plastic, ceramic, glass, liquid, and living cells [used for bio-printing]). • Select an approach to printing. • Select the software to prepare design files for printing.
Post-processing	• Remove remaining support structures and residues, polishing, sterilise and pack. • Final quality assurance testing.

Bio-printing, also known as bio-fabrication, is a 3D printing technique that combines biological materials and supportive biomaterials (e.g., scaffolds on which cells can grow) into so-called bio-inks. Despite some differences between 3D printing and bio-printing, they are largely similar albeit bio-printing is at a much earlier stage of research in human. Thus, bio-printing will not be discussed separately in this overview.

3D printing enables manufacturers to create devices matched to a patient's anatomy or devices with very complex internal structures. Three main types of 3D-printed devices can be distinguished according to the level of customisation: i) custom-made devices where a unique device or model fitted to an individual patient, ii) customisable devices where devices can be (mass) produced via a standard process and individualised according to individual parameters, and iii) standard devices where devices are 3D-printed due to its complexity or expenses to be built by other techniques.[4] The ability of 3D printing to create surgical instrumentation allows better visualisation of the anatomic characteristics for preoperative planning.[7] Also, guidance may be required to avoid damaging essential parts of the body for some complex surgical procedures; or anatomical defects may require custom prosthetics to repair damage as accurately as possible; or there is the desire to obtain a better aesthetic outcome. These needs have given rise to 3D-printed anatomical models, patient-specific guides, and 3D-printed prosthetics.[5]

3D printing concerns multiple surgical domains. Areas in research and development within surgical applications include orthopaedics (particularly knee surgery), maxillofacial surgery, neurosurgery, cardiac surgery, vascular surgery, otolaryngology, urology and general surgery, etc.[3, 5] Based on a 2016 systematic review of its clinical applications, orthopaedics has the largest share, with knee, hip, shoulder orthopaedics coming on top (Figure 1). This is followed by maxillofacial surgery, then cranial, spinal and cardiovascular surgeries.

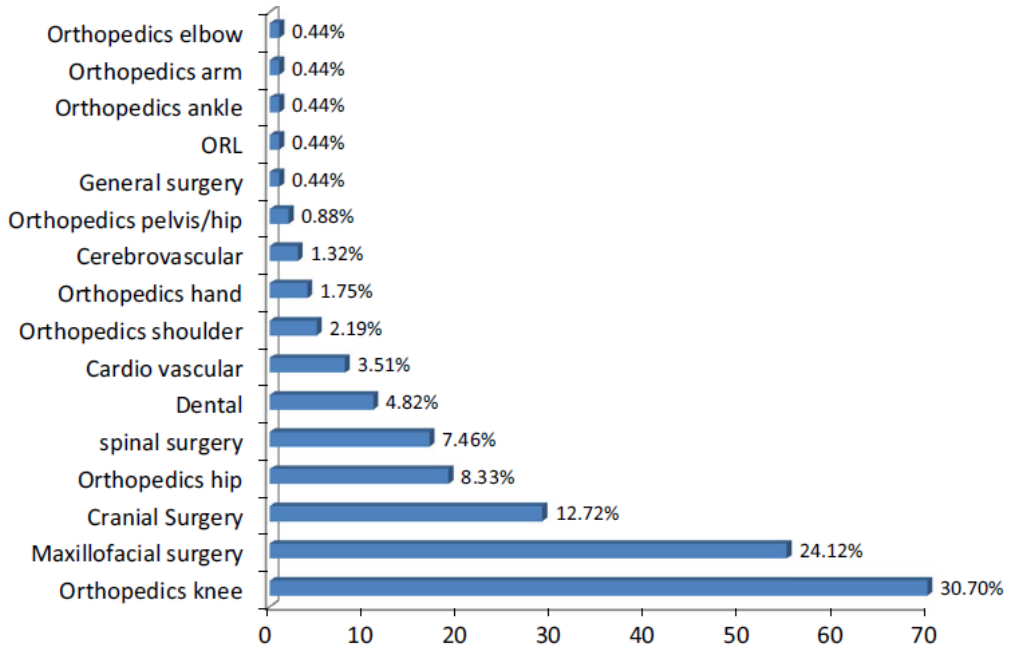

Figure 1: Overview of 3D printing in specific filed in 2016[5]

Among its clinical applications, 3D printing is most often used for i) surgical guides, from orthopaedics (guides for knee arthroplasties) to neurosurgery, spinal surgery, and maxillofacial surgery; ii) anatomical models for surgical planning in multiple disciplines or implant shaping in maxillofacial surgery; and iii) custom implants in cranial surgery and maxillofacial surgery.[4]

3D printing is anticipated as a disruptive technology to efficiently implement patient-specific therapies or to manufacture devices that cannot be constructed otherwise, with the capacity to radically change healthcare and revolutionise modern surgery in the foreseeable future.[6] A substantial logistical impact is also anticipated: fewer implants will need to be kept in stock and only one implant size needs to be available. This means that a much smaller set of surgical guides and associated instruments will be needed in the operating theatre, which in turn will reduce reprocessing as well as simplifying logistics within the hospital.[6]

III. Regulatory Considerations

Currently, 3D printing is generally regulated under the same frameworks for medical devices in most countries. However, as an emerging and potentially disruptive health technology, 3D printing presents a range of technical, legal and ethical challenges to existing regulatory frameworks as the conventional validation of mechanical performance may not be practical or sustainable for customised 3D-printed devices used for precision medicine.[8] This reflects the difficulties in designing a set of governing principles to regulate design control, quality control of raw materials, the optimal printing parameters and the production process, including correct functioning of the various software applications, reproducibility and speed.[3, 8, 9] Further, clinical data required by the regulators for approval of medical devices has been identified as a particular challenge for manufacturers to meet in terms of both quality and

quantity, as devices tailored to meet an individual's anatomical needs are confronted with the task of creating a sufficient volume of customised devices based on specific patient images.[8, 10] Some of the issues are discussed further in the Implementation section.

In both the USA and Canada, regulation of 3D-printed devices is subjected to regulatory framework for medical devices. However additional guidelines are developed recently for 3D-printed, especially moderate- to high-risk implantable devices. The guidelines are meant to supplement, not replace, other applicable regulatory guidance for medical devices.[1, 11] The additional information covered by the guidance includes i) technical considerations for relevant quality systems such as the design philosophy, validation of consistent performance, the accuracy of reproduction of patient-specific images, verification and validation of the software for design and printing; ii) manufacturing considerations such as raw material and any additives, biocompatibility testing on finished devices, processes and the post-processing steps, and iii) other information required for regulatory notifications and submissions. The guidelines generally do not cover the production of patient-specific devices, standalone software, and 3D bio-printed objects. Patient-specific devices would require a separate classification on an as-needed basis.

In Singapore, HSA regulates 3D-printed devices under its current regulatory framework for other medical devices which are classified into four risk classes. However, in response to the COVID-19 pandemic, a brief guidance on 3D printing of essential medical devices was published online addressing organisations who are considering 3D printing essential devices locally to address the increased demand and the overall interruptions to global supply chains.[12] The guidance highlights a number of key technical considerations for 3D-printed medical devices, which are consistent with the considerations mentioned by the FDA and Health Canada, including design, validation and manufacturing considerations. In addition, labelling should include sufficient information to identify or to trace the device. Note that healthcare institutions manufacturing 3D-printed medical devices for use only on their own patients do not need to register the devices.[12]

In Europe, the regulation of 3D-printed health technologies is complex and is governed by the core legal framework Medical Device Directive (MDD).[4, 13] Currently, there is no CE labelling for custom-made and customised 3D-printed medical devices, although customisable 3D-printed medical devices will have to comply with the same conditions as standard medical devices for market access. However, there is no consensus on whether 3D-printed models should be classified as medical devices or considered custom-made.[4] In addition, each component elements involved in 3D printing such as printer, raw material used, software and product specification (e.g. the set of data used by the software to print the device) may have its own regulatory implications. Hospital-made devices are exempt from some regulations provided that no equivalent product exists, the hospital is not mass-producing the items, and quality manufacturing standards are maintained. [4]

Similarly, Australia has recently finalised changes to the regulation of medical devices to better address the introduction of personalised medical devices, including 3D-printed devices. The new regulation adopts international definitions of custom-made medical devices by the International Medical Device Regulators Forum (IMDRF).[14] It creates a framework to

allow clinicians to produce low-risk devices without manufacturing certification, and regulates anatomic models in a way similar to diagnostic images.[15] The new personalised medical device regulations will commence on February 2021.

Of note, the complexity of printing biologic products warrants additional key considerations such as the compatibility of the printing process (e.g., cell viability/function, material properties), the integrity of the product after post-printing steps and the consistency of the manufacturing process (e.g., cell distribution, construct dimensions), and the biological activity and function of the finished products that may need to be evaluated.[10] Currently, these are not included in the existing frameworks.

IV. Current Development in Singapore

Stage of diffusion	Clinical applications
Investigational	Custom implants
Newly entered	3D-printed devices for COVID-19, anatomical models (?), surgical guide (?)
Nearly established	-
Established	-

According to the Economic Development Board, Singapore is striving to develop a high impact research and development hub for biomedicine innovations, acknowledging that 3D printing technology presents exciting new possibilities to transform manufacturing processes.[16] Under this initiative, the National Additive Manufacturing Innovation Cluster (NAMIC) was formed in 2015 to support the infrastructure, consolidate and foster collaboration, and accelerate translation and support adoption of 3D printing. 3D printing in medical technologies was identified as one of the key growing area under its recent Innovation Cluster programs.[17] Among the three additive manufacturing translation and capability development research hubs within NAMIC, the National University of Singapore's Centre for Additive Manufacturing (AM.NUS) is the main centre to bring innovative products to the field of healthcare that may improve patient outcomes and to apply ground-breaking 3D printing technology for personalised patient treatments.[18] Working with multidisciplinary expertise within NUS and clinicians from the National University Hospital, the centre focuses on five main areas of expertise including

- Surgical Instruments, Simulation & Prosthetics;
- Restorative Repair and Implants;
- 3D Bio-printing for Tissue Repair;
- AM Enabled Medicine; and
- Oral Health and Craniofacial Applications.

With the readily available infrastructure and resources, 3D printing is expected to be in the forefront of its applications in healthcare in Singapore. During the COVID-19 pandemic, a number of 3D-printed medical devices, including face shields or face masks, ventilator components, diagnostics, glove removers, etc., have been under evaluation or registered for

clinical use to help with the fight against COVID-19 in Singapore.[18] Some other examples of 3D printing under research relevant to this report include

- Novel titanium-tantalum alloy for better orthopaedic implants to suit specific patients (https://www.ipi-singapore.org/technology-offers/novel-titanium-tantalum-alloy-better-orthopaedic-implants);
- Osteoplug, a 3D-printed bio-resorbable polycaprolactone (PCL) bone graft implant, that enables the regeneration of a patient's skull bone tissue for bone healing (https://www.amchronicle.com/news/long-term-safety-and-efficacy-established-with-3d-printed-regenerative-implant/);
- 3D-printed human skin, which can be used to test the toxicity or irritation potential of a substance, and the penetrative qualities of active ingredients in different products (https://namic.sg/news/sg-based-startup-denova-sciences-collaborated-with-ntu-to-develop-the-future-of-bioscience-3d-printed-human-skin/).

V. Expected Impact on Healthcare

The most reported benefits of 3D printing in the literature are reduced surgical time, improved clinical outcome including surgical precision, improved final outcome, decreased risk of postoperative complications, and decreased radiation exposure, despite of a range of other perceived advantages such as gaining a better impression of the anatomic characteristics, preoperative planning in complex anatomies, the accuracy of 3D printing techniques (e.g., precise implant shape or precision and positioning of incision).[7, 9] Unfortunately, the subjective character and lack of strong evidence supporting majority of these advantages does not allow for conclusive statements.[4, 5] Even for the major argument for medical 3D printing − operation time, which is shown in most 3D printing applications, wide variances in mean time saved was reported between the different usages (e.g., 5.7 to 63 minutes). There were also arguments that the time needed to prepare the object is a limitation since the estimated time required for both virtual plan design and printing of an anatomic model varied with a range from 10 hours to a couple of weeks.[7] In addition, some also reported that the accuracy of the process was not satisfactory, together with poor mechanical properties and low solidarity particularly related to anatomical models.[7]

So far, surgical guides are the most commonly reported type of 3D-printed application, with relatively small number available for custom implants (Figure A1). 3D-printed surgical guides for oral and maxillofacial surgery, anatomical models for spinal and maxillofacial surgical planning seem to benefit the most from the technology.[5]

Anatomical models

Although anatomical models can be used on their own for surgery planning, implant shaping or patient selection, they are often used in combination with printed surgical guides. They have been used in the operating room as intraoperative references, with surgeons finding them particularly helpful because they could control positioning.[7] Systematic reviews of various study designs have suggested that 3D-printed models have been shown to be beneficial, in terms of improved surgical planning, clinical outcome, or reduced operation

time in orthopaedics especially complex hip replacements, and in cranial, spinal and maxillofacial models.[5, 6] Some benefits were also reported for planning for vascular procedures and complex congenital heart malformations. Further, anatomical models may also reduce the need for fluoroscopy during spinal surgery, reducing exposure to ionising radiation.[5, 7]

However a Belgium HTA report including only randomised controlled trials (RCTs) did not find convincing data that a procedure with 3D-printed medical devices is more effective or safer than a 'standard' procedure.[4]

3D-printed anatomical models have also been shown to improve patient understanding of the pathology and procedure, resulting in improved patient–doctor communication and greater patient satisfaction.[19-21]

Surgical guides or instruments

The use of 3D printing was reported in some studies to lead to less misplacements and errors during the surgical procedure, and decreased risk of post-operative complications.[7] Although there are some evidence supporting that surgical guides seem to reduce operation time and improve clinical outcomes for spinal and cranial surgery, no substantial difference in clinical outcome between patient-specific guides and standard instrumentation for total knee replacement was found, despite a slightly reduced operation time.[5, 7]

Data from RCTs in the Belgium HTA showed limited benefits for 3D surgical instrument in terms of operation time and no effect on mechanical axis malalignment for orthopaedic surgery, particularly total knee replacement. For other orthopaedic procedures or maxillofacial surgery, no convincing data demonstrate that a procedure with 3D-printed medical devices is more effective or safer than a 'standard' procedure.[4]

Custom implants

A systematic review of mixed study designs concluded that cranial custom implants seem to be accurate and to decrease operation time, while being associated with improved clinical outcomes. Similarly, 3D-printed trays and fixation plates also improved clinical outcomes and reduce operation time for maxillofacial surgery.[5] However, the HTA report from Belgium found no convincing data that a procedure with 3D-printed medical devices is more effective or safer than a 'standard' procedure. Also, based on available RCTs, no robust conclusions related to (long-term) safety of 3D applications for patients can be drawn.[4]

In summary, currently few studies have rigorously assessed the effectiveness of clinical 3D-printed devices, with discrepancies demonstrated between evidence from RCTs and observational studies.[4, 5, 22] So far, oral and maxillofacial surgery and the musculoskeletal system are leading the way in validating 3D-printed devices for clinical use.[22] It is also difficult to generalise many of the benefits reported for 3D printing across different settings, including reduced time in operating room, because many other factors must also be considered, such as the type of surgical procedure, the number of cases per year, the country, among others. Overall, efficacy and effectiveness of 3D-printed devices remain undetermined for the majority of medical fields. More rigorous assessments on their long-term outcomes are needed before these devices can become part of standard clinical practice.

VI. Expected Impact on Healthcare cost

Cost-related information on 3D printing is scarce. Typical costs of 3D printing 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 (e.g., fume hoods, ventilation set-up), staff training, equipment maintenance contracts, and personnel salaries.[3] The cost of 3D-printed parts also depends heavily on the manufacturing facility. Cheap desktop 3D-printers allow cheap 3D models and guides, but have less quality approvals and controls than commercial printer which can cost between US$2,210 to US$50,000.[5, 21] The reported additional costs per patient in a review varied widely from €150 to €700 depending on the application, with few mentioning direct preparation costs (CT, MRI, multiple prints, software, and computer) or the time cost involved in designing the model.[5, 7] This is supported by another review of 3D printing in vascular surgery indicating the cost of per replica ranged from US$4 to US$2,360.

Based on limited data and mixed results, the Belgium HTA concluded that there were no convincing evidence demonstrating that the use of 3D printing is cost-effective than standard treatment (details in Table A1 in Appendix).[4] The included studies gave varying results with increased, similar or decreased operating time and/or length of stay in a number of surgical settings, including highly labour-intensive, specialised surgeries (e.g., maxillofacial), and the associated costs.[4]

However, there is argument that the value of 3D printing may also be difficult to assess. For example, while the time required for the 3D printing process may greatly exceed the time saved in the operating room by using a 3D-printed model or device, the cumulative savings in operating room costs are likely greater than the additional expense required to produce 3D-printed tools.[21] It may also be difficult to generalise costs across different jurisdictions because of different practices.[3]

Given the current cost of 3D printing, and the often limited or unproven benefits, especially when the investment cost of the equipment and the time that surgeons devote to making scans and designing and producing the print are also taken into account, it is questionable whether currently 3D printing would be cost effective for most patients and clinical applications.

VII. Implementation Issues

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

Technical considerations

The quality of 3D-printed objects is heavily dependent upon the index imaging resolution followed by multiple production steps including digital processing to polishing of models to create realistic models.[3] To start with, 3D printing requires a minimum level of image and

resolution quality. With the many available software options, care is needed to prevent errors when converting data from one file type to another. Issues with accuracy (e.g., poor image resolution) and artefacts (related to CT being unable to scan metal) were also noted.[3, 21]

Currently, there are also concerns about the materials used for 3D printing, the limited availability of 3D printing compatible materials (e.g., common materials used in 3D printing are often not biocompatible), and the need for a better understanding of what type of internal structures of the material result in the best performance.[3]

As mentioned previously, although low-cost printers are available, 3D printing is more frequently being outsourced to commercial manufacturers as opposed to being printed in-house, resulting in increased costs. On the other hand, self-printing would subject to less quality controls and patients may not receive the support needed to maximize the safety and utility of such a device.[3, 5]

Regulatory and legal considerations

As mentioned in the Regulatory Section, the current regulatory frameworks for medical devices could create barriers for implementation of the technology. Currently, there is no consensus at the European level on whether 3D-printed models should be classified as medical devices or considered custom-made which are not subjected to any CE marking.[4] If the majority of 3D printing applications will not be considered as custom-made devices, manufacturers will have to provide sufficient evidence in their technical documentation, and undergo more extensive conformity assessments, which would impact on manufacturing costs and consequently implementation of the technology.[6]

Another concern is that the decentralised manufacturing process does not fit the current safety regulations which relies on centralised manufacturing processes and may not be sufficient if manufacturing occurs at point-of-care.[3] This also creates barrier for market access due to difficulty in generating clinical evidence on the performance of 3D-printed devices, and the long follow-up needed for particular applications such as joint implants. All these may have implications for the broader acceptance of the technology, as well as complicating its acceptance in the reimbursement system.[6]

Data ownership and privacy may present as a challenge for 3D printing, particularly for custom or patient-specific devices, as it requires individual patient data. It is not yet clear who will own the computer-aided designs, medical images, and final products, particularly when biological material is utilised. To ensure the privacy of patient personal data, 3D printing systems must also have adequate cybersecurity protocols in place, especially if hospitals outsource 3D printing to an external producer.[3, 4]

Further, 3D printing deviates from standard chains of production, distribution and use, making it difficult to apply the principles of product liability in the traditional sense − the producer is liable for any defect in its product. Multiple parties are involved in the production of 3D devices such as the surgeon who makes the initial design, the software engineer who develops the 3D design, the manufacturer of the printer or the material or the devices, etc.

It should be noted that there are also additional issues, including ethical considerations, related to the introduction of bio-printing,[23] but these are not discussed in detail in this report.

Reimbursement

The current state of evidence in terms of the quantity and quality of evidence, and unique features of 3D printing may present challenges in conducting comprehensive evaluations of the technology, particularly for health technology assessment. This may be considered a potential barrier to the adoption of 3D printing in health care.[3] Some specific considerations include inconsistency in regulatory requirements, questions around the amount and type of data collection needed to monitor long-term safety and effectiveness, challenges identifying specific manufacturers, lack of standardisation of the device due to customisation.[24] The IDEAL model (Idea, Development, Exploration, Assessment and Long-term study), which describes the steps to be followed in developing and assessing new invasive techniques and procedures, has been proposed for safe use of innovative 3D-printed high-risk devices and data collection.[4]

Given the different types of 3D-printed devices, different reimbursement frameworks may be needed. As highlighted in the Belgium HTA, 3D-printed custom implants do not require CE mark, thus can be used without its medical efficacy being demonstrated, at a cost to patients determined by the producers (at least partially). However, this can potential lead to large-scale dissemination of high-risk devices on the market, causing indirect pressure to reimbursement.[4] There is also the argument for the reimbursement for preoperative planning as this phase demands a great deal of time and effort in 3D printed devices than standard devices. However the argument should only stand if the services in the preoperative phase offer demonstrable added value to the patients compared to the alternative approach.[4]

Others

While cost is often identified as a barrier to introducing any new health technology including 3D printing, some reviews found mixed reporting about the costs of using 3D printing, with some reporting higher costs and some reporting lower costs associated with the use of the technology.[5, 7] The detailed information has been highlighted in the previous section. Regardless, the high start-up costs can indeed be an obstacle to the implementation of 3D-printing strategies due to the investment required for 3D printers, the related materials and software.

The production of 3D-printed medical devices involves multiple actors from different sectors, namely, software, 3D printer developers, material industries and hospitals. Given the multiple parties involved, the cooperation between the many stakeholders is complex. Surgeons play a huge role at the critical stage of preoperative planning to ensure the best outcome of the patients, but 3D software requires specific skills that most surgeons may not have. It is thus important that surgeons can accept the support of external technicians without fearing loss over their leadership.[7]

To enable surgical planning in multiple disciplines, it is advocated that centralised facilities for 3D printing in specialist healthcare institutions should be set up. This is not only resource

saving, but can also ensure that a substantial volume can be reached to maintain quality standard and the necessary technical/engineering expertise to complement the clinical expertise in a cost-effective manner.[6]

VIII. Expected Future Developments

An increasing number of specialties is anticipated to implement 3D printing in their daily practice with the increased use of silicon, gels and bio-absorbable materials, and decreases in production time with improved printing techniques.[7] Besides the printers and the raw materials, the software to convert images to printer instructions and to support users in performing surgical planning is also expected to be further developed. With the use of big data techniques and artificial intelligence, future software is expected to enable wider application of 3D printing with increased volume, at an acceptable price.[6]

In the Netherlands, there is ongoing work to set up a database of MRI scans and X-ray photographs for routine procedures like knee replacements. By matching these using computer-based learning techniques, it may be possible to design surgical guides based on X-rays alone, which is faster and cheaper than using MRI scans.[6]

As indicated the literature, few studies reported the use of 3D printing techniques in the fabrication of customised implants, as designing and producing implantable devices is much more challenging, which consistently requires the expertise of biomechanical engineers, than designing and producing anatomic models or surgical guides.[7] Currently, 3D-printed custom implants have been mostly used in osseous operations. The technical limits of 3D printing contribute to the rare application of this technology in soft tissue operations. This will very likely change with the development of bio-printing, which will provide additional possibilities for such operations.[7] Indeed, recent studies have reported on soft tissue applications in different clinical fields.[25]

Bio-printing has generated great interest for its potential role in reducing disease burden and health care costs.[23] Current research of bio-printing has been in a number of areas such as 3D printing of synthetic skin, replicating of heart valves or human ears.[26] The next step is printing organs that can be transplanted into human donors, or even printing organs in the body in-situ in the operating room. While the printing of full-scale biological organs is still a long way from being a reality, it has the potential to revolutionise medicine, making organ transplants and current synthetic artificial organs obsolete.[27]

Further, 4D 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. 4D printing is anticipated to provide benefits especially in the areas not covered by 3D printing technologies. The main limitation is that it requires extensive investment and support for transformation.[28]

IX. Additional Information

As COVID-19 pandemic spreads rapidly across the globe, some of the most radical technology innovations have emerged, including 3D printing, to address the challenge and shortages of critical medical supplies to fight against COVID-19. The most common applications of the technology include respiratory support apparatus such ventilator and its components, personal protective equipment (PPE) such as face masks and shields, printed equipment disinfection such as specimen collection kit, and environmental solutions such as hand-free door openers and glove remover.[17, 29, 30] The advancements in the development of commercially available antimicrobial polymers for 3D printing has been suggested to offer the possibility of rapid prototyping a wide range of critical medical devices during a pandemic, with some scientific evidence supporting the biocidal effects of copper nanocomposites and the enhanced antimicrobial behaviour of these composites in polymers.[31]

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Appendix

Figure A1: Overview of the usage of 3D printing techniques as percentage of total number of papers[5]

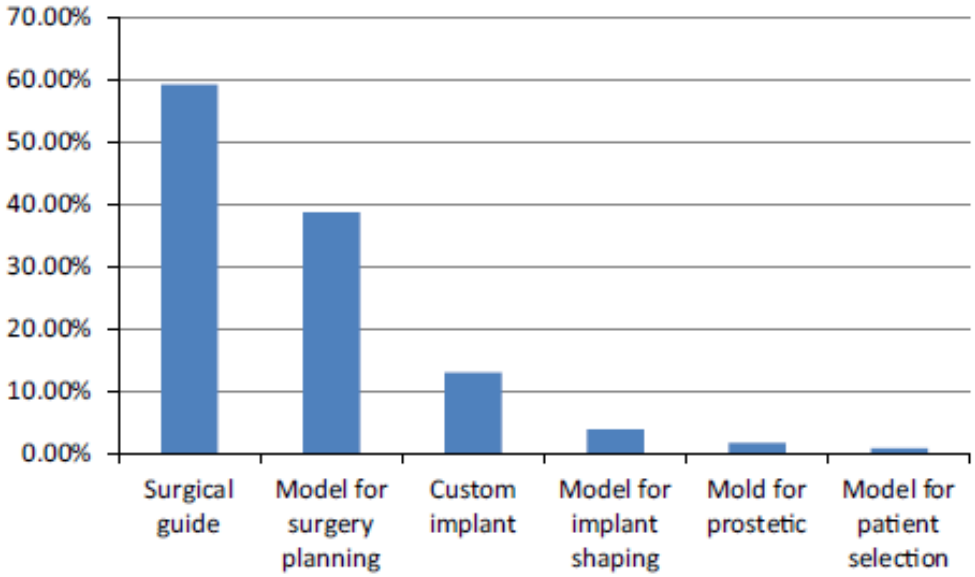

Table A1: Summary of the safety, time and cost results of the economic evaluations form KCE HTA report[4]

Author	Medical field	Purpose 3D-printing	Time horizon	Complication rate	(pre) operation time	Hospital length of stay	Cost
Tack et al., 2016[1]	Cardiovascular surgery	Surgery planning	1 year	Reduced †	-	-	Reduced or increased ‡
Rogers-Vizena et al., 2016[34]	Maxillofacial surgery	Surgery planning Implant shaping	Operative time	Equal §	Equal §	-	Equal or increased *
Yang et al., 2015[36]	Spinal surgery	Surgery planning	Hospital stay	Equal	Reduced	Equal	Increased
Lethaus et al., 2014[37]	Cranial surgery	Custom implant	Hospital stay	Reduced	Equal	Reduced	Increased
Baj et al., 2016[32]	Maxillofacial surgery	Surgery planning Custom implant	Hospital stay	-	Reduced	Reduced	Reduced
Resnick et al., 2016[33]	Maxillofacial surgery	Surgery planning Custom implant	Pre-operative time	-	Reduced	-	Reduced
Romero et al., 2015[35]	Dental	Surgery planning Implant shaping	Pre-operative time	-	Reduced	-	Reduced
Prisman et al., 2014[38]	Maxillofacial surgery	Surgery planning Implant shaping	Pre-operative time	-	Equal	-	Equal

*Note: Colored cells illustrate the results of the comparison 3D-printing versus standard technology. Green: in favor of 3D-printing technology. Red: in favor of standard technology. Orange: no difference between the technologies. † Based on expert opinion. ‡ Depending on the pathology considered. § The observed difference was found non-significant by the authors, this may also result from a lack of study power. * When accounting for the cost of the 3D model ($1000-2000).*