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Review article

Applications of three-dimensional printing in ophthalmology

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ABSTRACT

Three-dimensional (3D) printing is increasingly used to produce customized objects and is a promising alternative to traditional manufacturing methods in diverse fields, such as dentistry and orthopedics. Already in use in other medical specialties, adoption in ophthalmology has been limited to date. This review aims to provide an overview of 3D printing technology with respect to current and potential applications in ophthalmic practice.

Medline, Embase, and Internet searches were performed with “3D printing,” “ophthalmology,” “dentistry,” “orthopaedics” and their synonyms used as main search terms. In addition, search terms related to clinical applications such as “surgery” and “implant” were employed.

3D printing has multiple applications in ophthalmology, including in diagnosis, surgery, prosthetics, medications, and medical education. Within the past decade, researchers have produced 3D printed models of objects such as implants, prostheses, anatomical models and surgical simulators. Further development is necessary to generate optimal biomaterials for various applications, and the quality and long-term performance of 3D models needs to be validated.

1. Introduction

1.1. *Overview of three-dimensional (3D) printing*

1.1.1. *Definition of 3D printing*

Three-dimensional (3D) printing, also known as rapid prototyping or layered manufacturing, is a relatively new technology that has been increasingly used to create bespoke tangible and intuitive products from digital designs.[24, 29] Following the creation of 3D models in computer-aided design (CAD) software, 3D objects are produced by 3D printers via “layer by layer” accumulation. The phenomenal success of 3D printing in many fields ranging from automotive engineering to architecture has occurredover the past two decades. In medicine 3D printing has produced medical prostheses, surgical guides and

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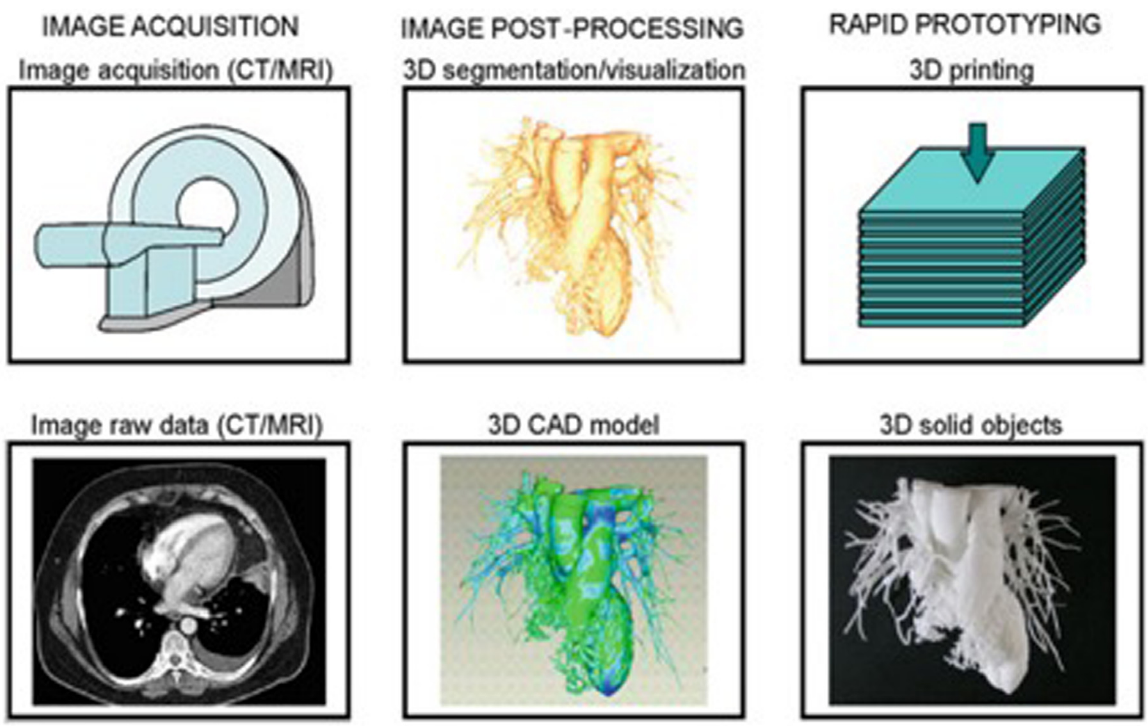


Fig. 1 – Images of the production process of 3D printing They showed the three main steps: image acquisition, image post-processing and 3D printing. Permission granted from Fig. 1 of.[61]

Table 1 – Comparison of different 3D printers and their applications. Permission granted from[11, 24, 29, 39, 61].

Printer	FDM	SLA	MJM	SLS	DMLS
Characteristics of 3D printers					
Base	Extrusion-based	Vat polymerization-based	Inkjet or Droplet-based	Power-based	Power-based
Material	Thermoplastic (heated plastic)	Photoreactive polymers	Acrylic photopolymers	Thermoplastic, plastics, metals, ceramics	Metal alloys
Cost	$ (US$50/kg)	$$$ (US$200/L)	$$ (US$300/kg)	$$$ (US$500/kg)	$$$$
Accuracy	++	+++++	++++	+++	++
Underlying technology	Print head	Ultraviolet (UV) laser	Print head	Laser (CO_2 laser beam)	Laser (solid-state Yb fibre laser beam)
Benefits	①Good strength ②Low cost	①Able to print large product ②Greatest accuracy ③Best surface finish ④Relatively light	①Highest precision ②Controllable transparency	①Able to print large product ②Good strength ③Variety of raw materials ④Accurate	①Without postprocessing ②Excellent printing quality ③Variety of raw materials
Drawbacks	①Time consuming ②Relatively poor surface finish	①Moderate strength ②Limited biodegradability	①Relatively weak strength ②Shape deformation	①Expensive ②Powdery surface	①Expensive ②Relatively small product size ③Slow
Main applications in medicine					
Prostheses	√	√	√	√	√
Surgical guide		√	√	√	√
Tissues implants	√	√	√	√	
Anatomical models			√	√	
Surgical instruments	√	√	√	√	

FDM = fused deposition modelling, SLA = stereolithography apparatus, MJM = Multijet modelling, SLS = selective laser sintering, DMLS = direct metal laser sintering; + = Level of accuracy; $ = monetary value; UV = Ultraviolet; CO_2 = carbon dioxide; mm = millimetre.

Table 2 – Comparison of the synthetic biomaterials and their potential applications. Adapted Table 3 of from[73].

Type	Advantages	Disadvantages	Applications
Metal and metal alloys (e.g.: gold, titanium, chromium, steel, cobalt, platinum)	①High mechanical strength ②Easy to fabricate and sterilize	①Corrosive ②Aseptic loosening ③Excessive elastic modulus	①Orthopedic implants ② Screws ③ Pins ④ Plates
Ceramics and carbon compounds (e.g.: calcium phosphate salts, glass, titanium)	①High mechanical strength ②Biocompatibility ③Corrosion resistance	①Difficult to mold ②Excessive elastic modulus	①Bioactive orthopedic implants ②Dental implants ③Artificial hearing aids
Polymers (e.g., PMMA, Polycaprolactone, polycarbonates, polyurethanes	①Biodegradable ②Biocompatible ③Easily moldable ④Ordinary mechanical strength	①Leachable in body fluids ②Hard to sterilise	①Orthopedic and dental implants ②Prostheses ③Tissue scaffolds ④Drug delivery
Composites (e.g.: dental filling composites, carbon fibre reinforced methyl methacrylate bone cement)	①Excellent mechanical properties ②Corrosive resistant	①Expensive ②Laborious manufacturing methods	①Prostheses ②Tissue scaffolds ③Drug delivery

PMMA = Polymethyl methacrylate.

Fig. 2a – Examples of 3D printed products in other disciplines. Fig. 2a: An Examples of 3D printed products in Dentistry. A 3D printed model used for the assessment of orientation and dimension requirements for teeth transplantation. Permission granted from Fig. 2b of.[5].

instruments, particularly for training and education, as well as generating surgical simulation models of specific cases so the surgeon can practice a procedure. Cardiac and orthopedic specialists have embraced this technology, and in ophthalmology, applications of 3D printing are emerging such that it is likely to impact eye surgeons over the next decade.

Although 3D printing is a branch of additive manufacturing technologies, the terms "3D printing" and "additive manufacturing" are usually interchangeable. Thus, in this review additive manufacturing, rapid prototyping and layered manufacturing will equate to 3D printing for simplicity and clarity.

1.1.2. *History of 3D printing*

In 1981, Hideo Kodama at the Nagoya Municipal Industrial Research Institute, Japan, described a technique to create 3D objects under ultraviolet rays using photocurable polymers by an additive method, but he did not finish the patent application.[4, 33] In 1984, Charles W. Hull invented, and in 1986 then obtained the patent for, the stereolithography apparatus (SLA). Subsequently he founded 3D Systems and produced the first commercial SLA printer in 1988, this being the first printer type used in the medical field. In 1989, two novel printers were patented: Carl Deckard patented Selective Laser Sintering (SLS), and S. Scott Crump patented Fused Deposition Modelling (FDM).

3D printing has been used in a diverse group of industries, with early reports in healthcare being notable. In 1994, SLA printing was used in the surgical planning of grafting a skull defect.[47] and in 2013 a 3D printed bioresorbable airway was implanted in a child with tracheobronchomalacia.[81] In oph-

Fig. 2b – Image of 3D printed hand prosthesis. Permission granted from Fig. 5 of.[10]

thalmology, uptake of 3D printing has been slower. Huang and Zhang.[23] in 2014 noted that "the use of 3D printing in ophthalmology has not had much impact, but an understanding of this new technology will be beneficial to ophthalmologists at present and in the future." Soon afterwards, a customized ocular prosthetic was produced in in 2015.[64]

1.1.3. *The production process of 3D printing*

Conceptually, in medicine, the production of 3D printed models involves image acquisition, image postprocessing, and rapid prototyping.[61] Image acquisition is usually carried out using a digital imaging platform to delineate the anatomy from a patient, most commonly by computed tomography (CT) or magnetic resonance imaging (MRI). Subsequently, the acquired images are converted and modified to stereolithographic digital models using segmentation software and computer aided design (CAD) software. Based on the obtained digital models, appropriate 3D printers are employed to print the desired tangible and physical objects by different additive methods.[13, 29] A schematic diagram of the 3D printing process is shown in Fig. 1.

1.1.4. *Common 3D printers*

Of the various 3D printing technologies that exist, the 5 most accessible and widely used printer types will be discussed. The main differences among them are the underlying additive techniques, sources of raw material, cost, and accuracy. Different types of 3D printers and their applications are summarized in Table 1.

In terms of the additive techniques and raw materials, FDM is based on extruding small beads of thermoplastic materials bonded to the layer underneath. Both SLA and Multi-jet modelling (MJM) are using photopoloymers, whereas SLA is actively using an ultraviolet laser, and MJM is using a piezo-based print head under ultraviolet exposure. In contrast, SLS and direct metal laser sintering (DMLS) are power-based, where SLS utilises small particles of metals, plastics, thermoplastic or ceramics that are fused by power-based laser. DMLS uses metal alloys exclusively. In terms of cost, FDM is the lowest, while the cost of DMLS is the highest among these printers, in terms of accuracy, SLA is generally regarded to produce the most accurate products . For generalizability, SLS and MJM have a wider range of medical applications, including prostheses, tissue implants, surgical guides, anatomical models, and surgical instruments.

1.1.5. *3D bioprinting*

The need for organ replacement and tissue regeneration is increasing worldwide.[18] With recent advances in cellular biology and tissue engineering, it is now feasible to recreate damaged tissue or even organs using 3D printers, with the chance of restoring function in these damaged structures. 3D bioprinting is defined as the assembly of living cells, growth-promoting factors, and biomaterials to accomplish one or more biological functions of native tissues.[51] The main difference between the traditional 3D printing and 3D bioprinting is the raw materials. In 3D bioprinting, the conventional materials including polymer, ceramic and metals are replaced by biological inks.[49] Biological inks or "bioinks" are mainly divided into two types, scaffold-based and scaffold-free. Scaffold-based bioinks combine living cells and scaffolds such as hydrogels and decellularized matrixes, while scaffold-free bioinks are made of cell aggregates alone. Specifically, 3D bioprinting using stem cells as a bioink has already been used in various systems including cardiovascular tissue, musculoskeletal tissue, neural tissue, hepatic tissue, adipose tissue and skin tissue.[57] 3D-bioprinted tissues have biological structures of various sizes (macro-, micro- and nanostructures) that can simulate the function and anisotropy of the original tissue.[19, 49, 75] Using 3D-bioprinted neural tissue as an example, it has helped facilitate research in both acute and chronic disease development. Meanwhile, it has also been used effectively in tumor research as scientists can reproduce the native tumor tissue from patients *in vitro* to mimic the tumor microenvironment, which allows the testing and improvement of current treatments and new treat-

Fig. 2c – Image of 3D printed right shoulder (anterior view). Permission granted from Fig. 5A of.[69]

Fig. 2d – Examples of 3D printed models of different parts of skull. Permission granted from the Regents of the University of California[A].

ments.[57] Bioprinting also has a promising potential in tissue regeneration because of its potential for customization, repeatability, and automation[52, 72]; however, the major barrier to 3D printed tissue or organ viability has been its vasculature. Solutions to this include the incorporation of endothelial cells or angiogenic growth factors in the 3D printed organ.[50]

1.1.6. Biomaterials

The term "biomaterials" refers to biologically inert substances that are used to replace or supplement the original human organs and tissues. They can be derived from both synthetic and natural materials. Currently, available synthetic biomaterials include biometals, bioceramics, biopolymers, and composite biomaterials. Natural biomaterials include collagens, gelatins,

Table 3 – Current classification of medical device by the FDA. Adapted from K, L, M, N.

Classification	Class I	Class II	Class III
Description	Lowest risk, under general controls	Moderate risk, subject to special controls	Highest risk, requiring premarket approval (PMA) to prove efficacy and safety
Example	Artificial eye[K]	Extraocular orbital implant[M]	Intraocular lens[N]

chitin, cellulose, fibrins, and decellularized tissue.[73] The selection of biomaterials varies depending on the needs of different material properties for different applications. An ideal biomaterial for 3D printing would be biocompatible, nontoxic, chemically stable, moldable, and accessible.[18] A comparison of a range of synthetic biomaterials and their potential applications is shown in Table 2.

1.2. *Applications of 3D printing in other disciplines*

3D printing has been utilised in Medicine since very early in the evolution of the field. Dentistry and orthopedics are the two disciplines with the most use of 3D printing technologies.[39, 55] Studies and reports of 3D printing applications have also been published in head and neck surgery,[22] plastic surgery,[11] cardiac surgery,[30, 37, 45, 67] and gastrointestinal surgery.[77] In this section the applications of 3D printing in dentistry, orthopedics, and head and neck surgery are introduced as a reference for its potential use in ophthalmology.

1.2.1. *Dentistry*

As a result of the developments of intraoral scanning technology, the improvements in printable biomaterials and the increased accessibility of 3D printers, 3D printing has dramatically changed dentistry over the past decade.[39] Examples of 3D printed models in dentistry can be found in Fig. 2A. Presently, two types of rapid prototyping have been widely applied in dentistry. These include photopolymerization techniques (such as SLA/MJM) and powder-based printing techniques (such as SLS/DMLS), which both can 3D-print various products including physical models, surgical guides, restorations and orthodontic appliances. Photopolymerization, especially MJM, is the commonest printing process in dentistry. It allows the products to be printed with various colors and physical properties, such as gum-like texture, nerve canals and realistic teeth.[68] Furthermore, a study has assessed the accuracy of 3D printed models by measuring intercanine distance, overjet, overbite, intermolar distance, tooth size, and arch length.[28] The findings suggested that the accuracy of models was not satisfactory. Therefore, future studies were deemed necessary to evaluate the accuracy of 3D printed products, to ensure they are optimal alternatives to conventional methods.

1.2.2. *Orthopedics*

In orthopedics, 3D printed prostheses such as a hand prosthesis (Fig. 2B) are gaining popularity for the treatment of children with impaired limb functions owing to its cost-effectiveness, lightweight and durability. In addition, rapid modifications and replacement of prostheses can be achieved to fit the changing demand for children's growth.[10] Furthermore, in natural disaster emergencies such as an earthquake, 3D printing allows the manufacture of splints, crutches and prostheses on site without requiring shipping from elsewhere. Being able to do this on site in a developing country has the potential for timely treatment in a cost-effective way.

3D printing is also used for surgical planning. Sheth and coworkers[69] demonstrated the successful use of 3D printed models in the preoperative simulation of surgeries for patients with anterior shoulder instability (Fig. 2C). Compared with traditional 2D imaging, the 3D printed models can help orthopedic surgeons understand better the amount of bone loss, lesion depth, abduction degree, and external rotation. These features are helpful in choosing the best operative procedures, the number of suture anchors, and the placement of incision placement. As a result, reduction in intraoperative time, intraoperative blood loss, anesthetic dosage, and complication rates can be achieved with the help of 3D printing techniques. 3D printing is also beneficial for education and the study of anatomy because of the scarcity of real specimens due to reducing rates of body donation and prosection.[1]

Although short-term outcomes of 3D printed implants and prostheses have been reported to be satisfactory, in terms of functional restoration and lack of complications, long-term studies will be necessary to validate the adoption and expansion of such applications of 3D printing in orthopedic practice in the future.[1, 10, 62, 69]

1.2.3. *Head and neck surgery*

The use of 3D printing in head and neck surgery has been dominated by bony reconstructions. Klammert and coworkers demonstrated that 3D printed calcium phosphate implants could be used for patients who needed reconstruction of cranial or maxillofacial defects.[31] Compared with conventional prefabricated titanium implants, 3D printed models have the advantages of patient-specific design, increased accuracy, and reduced cost.

In terms of the efficiency of 3D printing in facial reconstruction, Strong[H] and coworkers successfully printed different parts of the skull in a single day (Fig. 2D). Given the anatomical complexity of maxillofacial reconstructive surgeries, 3D printed high-resolution models allow surgeons to conduct detailed surgical planning more efficiently and accurately. In addition, trainees as well as experienced surgeons can learn from the patient-specific models as templates for delicate or new surgical procedures. 3D printed models are crucial not only for education, but also for decreasing the amount of time for the surgical procedure. Practice and plan-

Table 4 – Examples of the cost of 3D printed models. Referenced to [11], [12], [40], [45], [53], [67], [69], [74], [76], [82] B and I.

Discipline	Item	Cost
Ophthalmology	Ocular foreign body simulator[40]	US$580
	Anatomical orbital model[B]	≤ €300
	Artificial eye/ prosthesis[H]	US$40 (student's prototype) US$4000
Orthopedics	Glenohumeral model[69]	US$150
	Adult pelvis[69]	US$1,100
	Prosthetic hand[82]	US$50 (materials cost only) US$4000 (fully assembled hand)
	Prosthetic hand[74]	US$500
	Bone reduction clamp for hand fractures[11]	US$75 (FDM) US$1200 (DMLS)
Cardiology	Pulmonary artery[45]	US$100
	Pulmonary artery with flexibility and ability for catheter insertion[45]	US$700
	Internal carotid artery (commercial version)[53]	US$250 (disposable component) US$4000 (reusable component)
	Cardiac structures[67]	€200 - €400
Otolaryngology[76]	Septoplasty/ Rhinoplasty surgical simulator (single use)	CAN$186
	Skull base surgery trainer	US$900
	Endoscopic endonasal skull base drilling	US$500 (materials cost only)
	Laryngeal simulators	US$2.08-6.97
DNA printing[12] (predicted costs)	Protein	US$500
	Human genome	US$2.2 billion
	Plasmid	US$5000
	Bacterial genome	US$1.5 million
	Yeast genome	US$4.2 million

€ = Euro

Table 5 – Applications of 3D printing technology in orbital diseases. Permission granted from Table 1 of[63].

Applications	Indications	Purposed 3D printed models	Common materials	Suggested 3D printers
Implants	①Orbital fractures ②Orbital tumors ③Anophthalmic socket syndrome	①Orbital implant ②Positive or negative mold	①Titanium ②Resin	①SLS ②FDM ③SLA
Prostheses	①Exenterated orbit ②Anophthalmic socket	①Positive or negative mold	①Resin (e.g.:acrylonitrile butadiene styrene)	①FDM
Anophthalmic socket conformers	①Congenital anophthalmic and microphthalmic socket ②Contracted anophthalmic socket	①Conformer	①Resin (e.g.: polymethyl methacrylate)	①SLA
Surgical planning	①Orbital and craniofacial trauma and tumors ②Developmental disorders, e.g., hypertelorism, hemifacial microsomia	①Skull	①Resin (e.g., acrylonitrile butadiene srtrene, plaster)	①SLA
Surgical simulators	①Orbital decompression ②Orbital reconstruction surgery	①Orbital bone with or without soft tissues ②Skull base	①Resin (e.g.: polylactic acid, silicone)	①FDM ②SLS

3D = three-dimensional; FDM = fused deposition modelling; SLA = sterolithography apparatus; SLS = selective laser sintering ning with a 3D printed model may add time preparing for surgery, but leads to less time in the operating room.

3D printing has already been effectively applied in many medical disciplines, with agreement that 3D printing is feasible and promising in healthcare. Crosspollination of ideas and techniques from different medical disciplines has the potential to aid overall progress.

1.3. Regulation of 3D printing

Legal and regulatory hurdles exist which have limited the widespread use of 3D printing in the medical field. In the US, all 3D printed biologics, drugs and medical devices are regulated and managed by the Food and Drug Administration (FDA). According to the current classification of medical devices by the FDA, 3D printed products are classified as Class I, II, or III (Table 3) based on the level of risk[L]. Class I incorporates devices with the lowest risk to the user and are under general controls (e.g., artificial eyes[K]). Class II are more invasive and therefore subject to special controls (e.g., extraocular orbital implant[M]). Class III is considered as highest risk product because of their invasiveness, requiring premarket approval to prove efficacy and safety (e.g., intraocular lenses[N]).

The first 3D printed oral drug, Spritam (levetiracetam), was approved by the FDA for the treatment of seizures in August, 2015.[38] Its design contains layers with voids to aid rapid dissolution. In terms of medical devices, as of 2017 the FDA had approved about 80 3D printed medical devices. None of these were Class III devices that carry the highest risk and require premarket approval by the FDA. It appears that it is the product rather than the route of production that is of greatest importance to gain approval.[7]

In December of 2017, the FDA released guidance for 3D printing entitled "Technical Considerations for Additive Manufactured Devices"[O] or industry and their own personnel. The guidance was divided into two aspects: design and manufacturing and device testing. The first part focused on device design, material controls, software workflow, process validation, postprocessing, acceptance activities, and quality data. The second part included description of the device, mechanical testing, dimensional measurements, material characterization, removing manufacturing material residues, and sterilization, and biocompatibility.

Legal liability of 3D printed products will vary in different jurisdictions. Broadly, tort liability is either based on negligence, which is fault based, or strict liability, in which a manufacturer is liable regardless of fault.

1.4. Cost of 3D printing

1.4.1. Overview

The global market for 3D printing was estimated to exceed US $6 billion in 2019,[24] while the worldwide bioprinting market was estimated to reach US $1.82 billion by 2022.[26] Examples of the cost of 3D printed models are shown in Table 4.

1.4.2. Total cost of 3D printing

Currently, the cost of 3D printing is one of the obstacles to its widespread use in medical field. The cost of 3D printed product usually is assumed to be cheaper than the conventional product because of low-cost hardware (3D printers and materials); however, this is not the only expense in 3D printing industry. The total cost of 3D printing should also account for software (design and postprocessing), regulatory cost for medical device, and labor cost (design, operation, training, maintenance, and engineering). Among these, design accounts for the largest part of the cost because only experienced designers can create medical-grade 3D printed products.

1.4.3. Patent expiration

As 3D printing technology has been available for more than 30 years, some of the patents have expired. The U.S. Patent and Trademark Office (USPTO) sets the current patent term at 20 years from the patent application date. Currently, over 12,000 patents are linked to 3D printing, and many of them are related variously to methods, processes, systems, software and designs.

Expiration of some of the key original 3D printing patents has paved the way for cheaper manufacture and broader development. Since 2002, about 225 3D printing patents have expired[E], of which 16 were related to the 3D printing process, including FDM, SLS and SLA. Hence, the earlier 3D printing technologies are more affordable for individuals. Owing to advancing technology and reducing prices, domestic 3D printers are now available in the United States for less than US $1000.[24] Unfortunately, many of these printers are only capable of producing small products, limiting their widespread use.

1.5. Aims and objectives of this review

3D printing has been widely used in various early adopter disciplines such as dentistry and orthopedics; however, current applications of 3D printing in ophthalmology remain limited. Hence, we will provide an overview of 3D printing technology and discuss the current and potential applications of this technology in ophthalmology. In addition, we discuss limitations and future research directions of 3D printing in ophthalmology.

2. Discussion

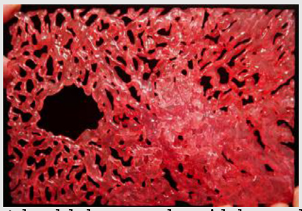
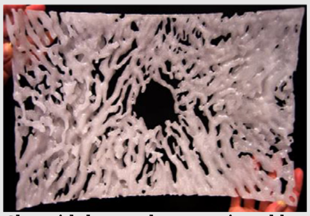
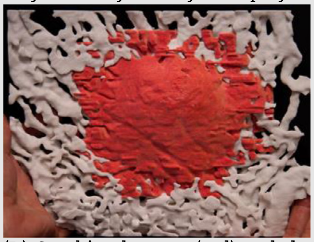
Applications of 3D printing in ophthalmology will be categorized with respect to the potential use: diagnosis, clinical devices, surgery, drugs, and education. As well as these areas, the quality assurance, limitations, and future work of 3D printing in ophthalmology will also be addressed. Using orbital diseases as an example, a summary of applications of 3D printing technology includes implants, prostheses, anophthalmic socket conformers, surgical planning, and surgical simulators is shown in Table 5.

2.1. Applications of 3D printing in ophthalmology

2.1.1. Diagnosis

Diagnostic imaging is one of the cornerstones of ophthalmic practice. Currently, optical coherence tomography (OCT), especially OCT angiography (OCTA) and spectral-domain OCT (SD-OCT), has revolutionized the management of retinal and choroidal vascular diseases and tumors. With the advance of

Table 6 – 3D printed models of choroidal vessels and tumors. Permission granted from Fig. 2B, 3A-C of[46].

Examples of 3D printing	Printer duration	Result / observations
 A health human choroidal vessels printed by transparent red resin (SLS)	Unknown (120 mm × 75 mm × 8 mm)	① More round and bulky peripaillary vessels ② Few recognizable small branching vessels ③ Extremely compact and dense foveolar choroidal vessels
 Choroidal vasculature printed by transparent polycarbonate (FDM)	45 hours (210 mm × 390 mm × 23 mm)	① Dense choroidal vascular archs were surrounding the optic nerve ② The optic nerve could be recognized as a vascular void area ③ Vessels were radial convergence of towards the optic disc ④ Vessels became thinner and flattened to the periphery region
 Choroidal tumor printed by UV light resistant acrylnitril-styrol-acrylat-copolymere (FDM)	6 hours (90 mm × 120 mm × 8 mm)	① Most of the vessels were obliterated and displaced by the tumor
 (D) Combined tumor (red) and choroidal vessels (white) printed by Two-color polymer gypsum power (FDM)	8 hours (170 mm × 245 mm × 25 mm)	① It showed the interdigitation between the relative avascular tumor and choroidal vessels

SLS = Selective laser sintering; FDM = Fused deposition modelling; UV = Ultraviolet

3D printing, 3D printed models help doctors to visualize and magnify the spatioanatomical details of the vessels. For example, Maloca and coworkers[46] built several 3D printed models of normal and pathological choroidal vessels, and models of pigmented choroidal tumors with and without choroidal vessels (Table 6). Through analyzing 3D printed models, the anatomical details of choroidal vessels, as well as their relationships with the tumor, were noted, revealing the interdigitation border of the tumor and surrounding vessels. The 3D viewing of choroidal vessels may be especially useful in choroidal inflammatory and infiltrative diseases as well as a new way of documenting choroidal melanoma growth, treatment planning and judging the effects of therapy.[17]

Despite the promise of 3D printing in the report of Maloca and coworkers,[46] there remains some limitations and challenges. The combined model of the tumour and choroidal vessels was made of polymer gypsum powder, which was brittle and prone to damage. Moreover, the layers of choriocapillaris that were not captured by OCT could also not be 3D printed.

2.1.2. *Clinical devices*

2.1.2.1. *Implants* The benefits of customized implants include[1] alleviation of the shortage of donor organs,[2] improved surgical outcomes due to reduced surgical time and[3] customized disease-specific or size-specific implants.

Cornea One of the most frequently transplanted organs is the cornea. In the United States, over 40,000 patients require corneal transplantation every year[71]; however, due to the shortage of donor material, there is a constant search for new source of transplantable tissue. Features of the cornea,

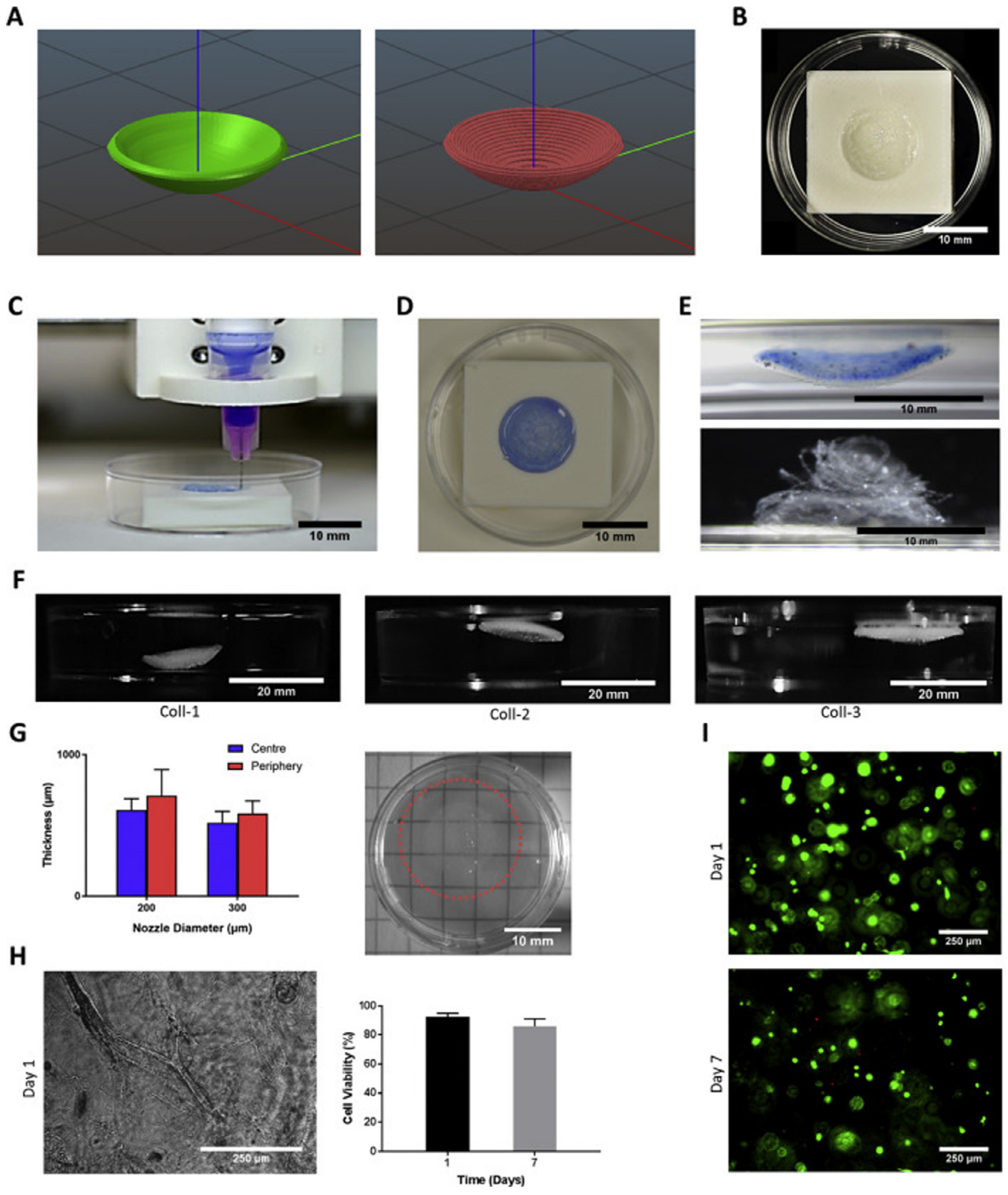


Fig. 3 – Images of the manufacturing process of 3D printed cornea Legend: Fig. 3A: The 3D printing process of cornea. The cornea is stained with dye (trypan blue) to make it visible. Fig. 3B, C: Images of 3D printed cornea before and after incubation. Fig. 3D: The corneal structures begin to unravel 24 hours after the initial printing because of the combination of keratocytes and alginate bio-ink. Permission granted from Fig. 2C-E of.[25]

including low-level metabolism, avascularity, optical clarity and homogeneous structure, make the 3D printed cornea an attractive option. Isaacson and coworkers[25] (Fig. 3) manufactured the first 3D printed cornea using collagen-based bioink combined with corneal keratocytes. In a laboratory setting, the viability was as high as 90% on the first day and 83% at the seventh day following the initial printing process.

Ongoing prospective research in 3D printed cornea is proceeding with the manufacture of a 3D printed human cornea using the patient's stem cells[J]. The goal of this study was to produce a human-like corneal stroma by using inert collagen and the patient's own stem cells to eliminate the immune rejection in patients receiving cornea transplantation. The method of synthesizing a collagen matrix of cornea and printing the patient's stem cells over the cornea by rapid prototyping is still undergoing investigation. Similarly, another study has reported that the hoki fish scale, immunologically inert for humans, was a potential novel source of printable

Table 7 – Comparison of the characteristics between Ridley Lens and 3D printed Lens. Permission granted from Table 1 of[14].

Characteristic	Ridley Lens	3D printed Lens	Difference (%)
Diameter (mm)	8.35	8.10 ± 0.01	3.0
Thickness (mm)	2.44	2.50 ± 0.01	2.5
Weight (mg)	108	117	8.3
Anterior radius of curvature (mm)	17.7	14.63 ± 0.69	17.3
Posterior radius of curvature (mm)	10.69	10.88 ± 0.22	1.8
Optical transmission 400 to 700 nm	75%	75%	0.0
Back focal length in air (mm)	12.676	14.1± 0.4	11.2
Ridge	Rounded	Square	-
Optical index	1.49	1.53 (optical parts)	2.7
		1.49 (central substrate)	0.0
Anterior surface analysis: RMS	0.346	0.762	120.2
Posterior surface analysis: RMS	0.273	0.959	251.3

RMS = root square; mm = millimetre

Fig. 4 – Image of 3D printed Ridley lens: the 3D printed lens shows good transparency but some notable surface roughness with irregularities. Permission granted from Fig. 1 of.[14]

collagen for 3D printed cornea.[71] Despite these promising preclinical studies, further research including clinical trials are required to assess the efficacy and safety of 3D printed cornea before entering the implant market.

Intraocular lenses Another application of 3D printing in ophthalmic surgery is the intraocular lens (IOL), to replace current lens implants during cataract surgery. In a nod to history, Debellemaniere and coworkers[14] reproduced the original model Ridley IOL (Fig. 4) using an online 3D lens printing service (LUXeXceL Group BV, Kruiningen, Netherlands) from CAD drawings. There was good transparency and optic index compared to the Ridley lens (Table 7).

Patient-specific IOL production allows the correction of specific refractive errors such as irregular astigmatism and the modification to account for unusual anatomical peculiarities. The 3D printed lens successfully mimics the physiological process of embryonic lens formation, which is also a layer-by-layer process; however, several challenges need to be overcome before such lenses enter mainstream use.[14] The anterior radius of curvature and the back focal length of the 3D printed IOL were significantly different from that of the traditional lens. Surface analysis of 3D printed IOLs revealed notable surface roughness with irregularities, which suggests that the 3D printed lenses are still not at a sufficient level of quality to consider implantation at this stage. The accuracy of the optical power of 3D printed IOLs is also not as good as that of the Ridley lens. Optimal biomaterials for printing IOLs are still under investigation. Current suggested materials include PMMA-like materials, hydrophilic materials, silicone, soft and wet hydrogel composite, but as of now, none of these are ideal.

Bionic eye Electronic components such as batteries, capacitors, diodes, and sensors have been fabricated with 3D printing technology for use in biological systems such as artificial electronic skins. Optoelectronics, the manufacture of light-sensitive signal transducers, has also been the subject of 3D printed technology to restore vision. Park and coworkers [C] successfully produced light receptors on a hemispherical surface using 3D printing techniques, which led to the first 3D printed prototype of a bionic eye (Fig. 5). In this report, the 3D printed hemispherical photodectector array was capable of detecting images with a wide field-of-view. A glass cone, silver nanoparticles, several layers of semiconductive components and liquid metal were utilized to fabricate the whole model, which took about an hour to print; however, to complete future studies in this field, it is necessary to improve the performance of the 3D printed photodetectors to match current commercial photodetectors, to improve the image sensitivity and resolution; to develop customizable photodetectors, and to monitor for toxic effects and physiological changes (e.g., blood oxygen and pulse rate) when such devices come to human trials.

Retina Apart from the cornea, 3D bioprinting is considered as a promising technique for the regeneration of human retina, despite it being a complex structure consisting of at least 60 different functional cell types.[48] Lorber and coworkers[43] used a piezoelectric printer in order to 3D-print two types of adult rat retinal cells, retinal ganglion cells and glial cells, as shown in Fig. 6. During the printing process and cell culture, no adverse effect on the shape, viability, or growth of the cells was found. Hence, this study suggested that the retinal tissue, one of the most complex in terms of ophthalmology, may be an area where 3D bioprinting will be part of a promising fu-

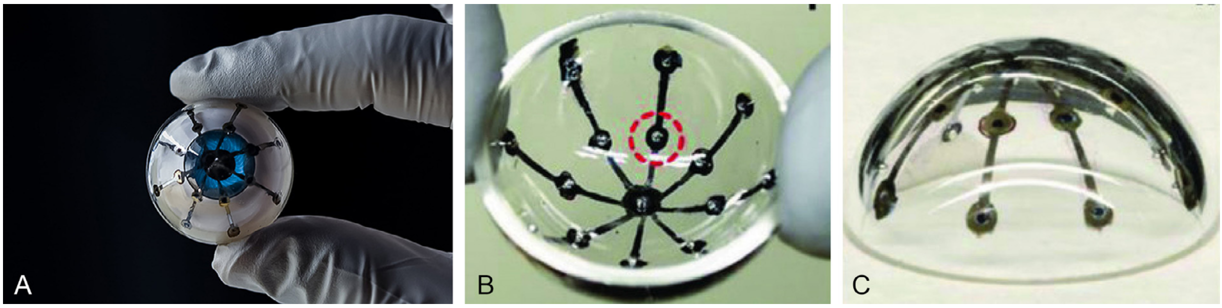


Fig. 5 – Image of 3D printed concentric photodetector array Legend: They are image sensors printed onto the inner surface of a hemispherical glass dome. Permission granted from K and Fig. 5B-C of.[59]

ture in regenerative medicine. Although there have been encouraging first steps, further research and development needs to take place in order to successfully fabricate complex multicellular tissues. One suggested approach to accelerate this development is to 3D-print a non-cellular hydrogel scaffold and then seed retinal neuronal cells (ganglion cells and glial cells).[20] In terms of the result of another Lorber study,[44] the 3D printed retinal cells were shown to preserve their viability and certain phenotypic features after the printing process, although the number of cells was reduced because of sedimentation within the print head. Future success may require not only the survival and viability of neuronal cells, but also the presence and function of a viable vascular supply. Kolesky and coworkers[34] created a customised 3D bioprinter with 4 independently controlled print heads, which was developed to print vascular tissue using multiple inks. Therefore, this innovative 3D printer can be applied to create models with several cell types within a multilayer tissue, which can better simulate the original function of the native tissue. Lorber and coworkers[44] suggested that efforts in 3D printing of the retina need to be on multiple fronts. The aim is for the generation of the many different cell types, their viability and spatial arrangements, forming appropriate interlayer horizontal and vertical connections, demonstrating function and allowing long-term survival by construction of a vascularized retinal structure.

2.1.2.2. Ocular prostheses Ocular prostheses are crucial for patients who have congenital malformation, suffer severe ocular trauma that requires evisceration or enucleation for a tumor. The current manufacture of ocular prosthetics is an artisanal, hand-made process that has been practiced relatively unchanged for the last century. This makes eye prostheses expensive, while only limited choices of type of ocular prostheses are available in the market. Acrylic ocular prostheses are time-consuming to produce and may occasionally lead to allergic reactions, while Plexiglas eye prostheses are relatively durable, but have a glassy appearance. Both are usually made after the socket is molded with an alginate impression, which can be an invasive and unpleasant process. Subsequently, the eye is manually painted with the color of patient's iris. Features such as the episcleral veins are reproduced by gluing silk thread fibres onto the prosthesis. In contrast, 3D printing of prosthetic eyes would likely cut manufacturing times substantially. Ruiters and coworkers[64] developed a patient-specific ocular prosthesis using 3D printing technology for a 68-year-old man with anophthalmos secondary to evisceration (Fig. 7A), which was shown to successfully fit into the patient's eye socket (Fig. 7B). It was a plain prosthesis, and post-processing was performed to paint the iris and scleral details for cosmetic acceptability. Similarly, the technique of Alam and coworkers,[3] which took a CT scan of an impression mould of the socket to 3D-print a white artificial eye, had to be hand painted by an ocularist.

Several methods have been used to mould the shape of the surface that will wear the prosthesis. Ruiters and coworkers[64] used cone beam CT scan with the disadvantage of radiation exposure. In some pilot studies, corneoscleral topography with the eye surface profiler (ESP) was used to measure the ocular shape instead of alginate molding[27,66] and anterior segment optical coherence tomography (AS-OCT) scans have also been developed for this purpose.[65]

To determine the optimal material for the scleral cover shell prosthesis, polymethylmethacrylate (PMMA) and polylactic acid (PLA) were compared.[66] (Fig. 7C). PMMA is a transparent thermoplastic material, which was first used in contact lenses and scleral prosthesis. However, the surface roughness of 3D printed contact lenses remains a concern because it may cause discomfort by eyelid friction. On the other hand, PLA is a translucent biodegradable material that is generally made of renewable materials such as corn starch. The disadvantage of PLA is that it showed a slight shrinkage after 3D printing, and it was difficult to handle in contact with water because of its high solidification and cooling speed, which may lead to damage or stretch on the product. As such, further studies are necessary to begin to understand the optimal materials for 3D printed ophthalmic prostheses.

Recently, a team of Korean researchers[32] developed a semi-automated protocol for 3D printed artificial eyes (Fig. 7D). A light intensity 3D scanner imaged the socket, replacing the current need for alginate impression molding. A plain white prosthesis was 3D printed according to the shape obtained from the light scanner. A photograph of the fellow eye was then mirrored, 2D-printed and transferred onto the plain prothesis. Both traditional and innovative 3D modelling require approximately 1 hour from an impression mold to a 3D printed model. Moreover, with this innovative method, human effort was considerably reduced compared with the traditional method as it is an automated process. Also, with

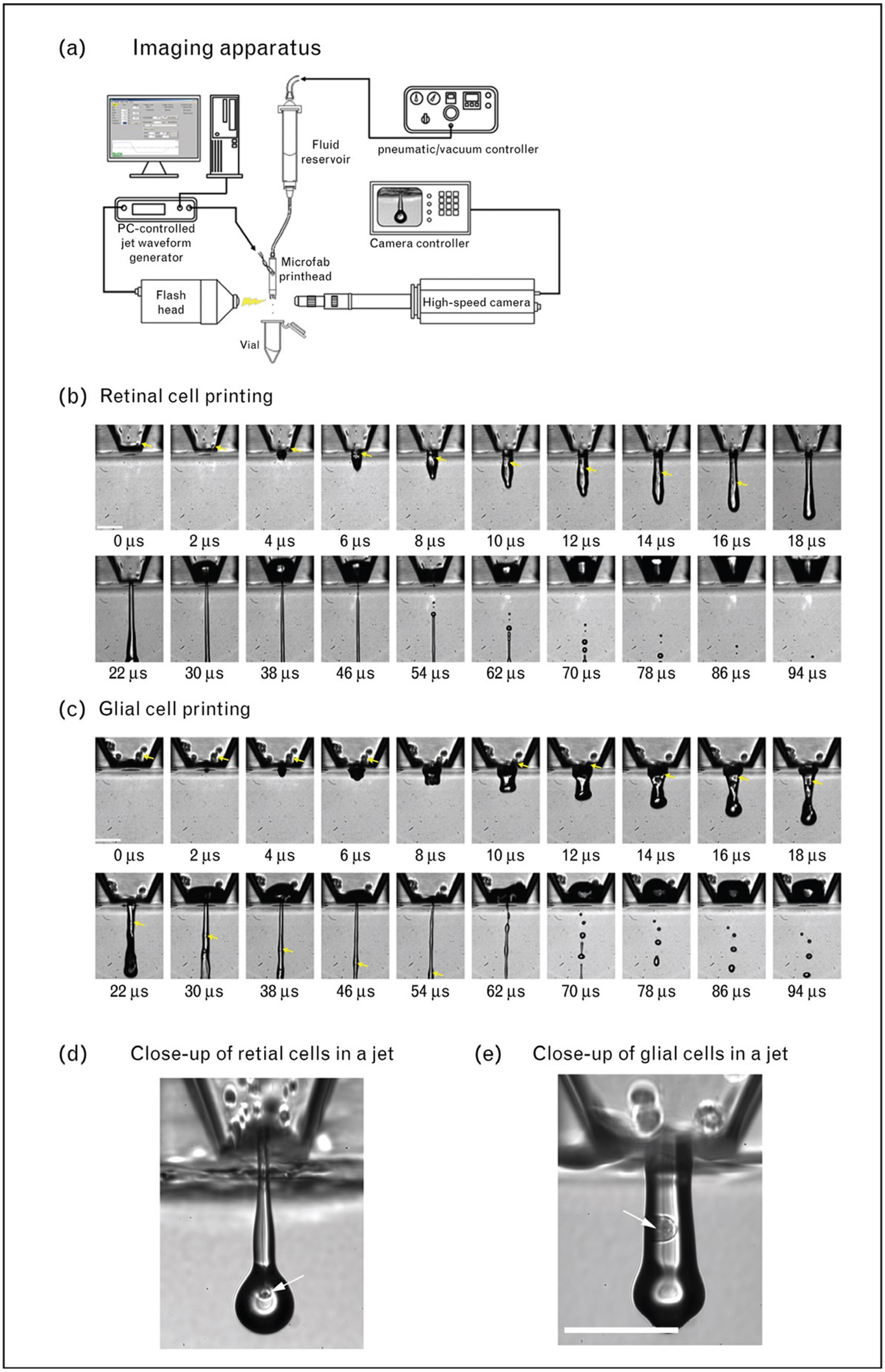


Fig. 6 – The process of retinal cell and glial cell by 3D printing Fig. 6A. A schematic image shows the imaging apparatus used for 3D printing of retinal glial and retinal cells. Fig. 6B, 6C, 6D, 6E: Images sequences and magnified images of retinal cell printing and glial cell printing. Scale bar: 100 μm. Permissions granted from Fig. 1 of.[44]

Fig. 7a – Images of ocular prosthesis Fig. 7A: Image of anophthalmic cavity molds of a patient. The left model is a traditional mold which made of polyvinyl siloxane material; the right model is produced by 3D printing using resin. The traditional mold is slightly larger than the 3D printed mold in size. Permissions granted from Fig. 3 of.[64]

Fig. 7b – Images of a patient with 3D printed mold (left) and 3D printed prosthesis (right). Permissions granted from Fig. 4 of.[64]

stored digital data, replacement prostheses may become easier and readily accessible to fabricate.

The most difficult part in 3D printing of an artificial eye is to make an accurate, consistent and perfect match with size and color to the existing eye. A fully digital 3D printed ocular prosthetic has been developed, using anterior segment OCT to scan the anophthalmic socket[65] and the fellow eye. Anatomical information of the normal eye was then 3D printed in full color (Fig. 8). This fully digital 3D printed prosthetic eye is a true anatomical biomimic and a more realistic prosthesis with clear definition and real depth to the pupil[G]. Unlike the traditional hand-painted prosthesis, this 3D printed one requires an OCT scan of the socket instead of an invasive mold, as well as OCT scan and color photograph of the normal fellow eye – both taken on the same anterior segment OCT scanner (Tomey CASIA X, Tomey Corporation, Nagoya, Japan). The manufacture time can be reduced from 6 weeks in the conventional way to 3 weeks in 3D printing, once the full process is complete. Hence, a better-quality prosthesis is manufactured with a faster period of production time. Although the production time is reduced, the overall cost of 3D printed artificial eye is comparable to conventional artificial eye, due to costs of development and design.

Commercial ventures have now produced 3D printed ocular prostheses in several pre-defined sizes without tailored irises, which are necessarily not customised to the individual's eye requirements[D]. Each 3D printed eye is manufactured from the same system, which made the cost drastically reduced to £100.

2.1.2.3. Corneal models for contact lens fitting Rigid gas-permeable contact lenses (RGPCL) have been well established as a treatment for patients with high degree of refractive error, keratoconus, and following corneal transplantation. Nevertheless, in some cases, RGPCL fitting is difficult for patients with an irregular corneal surface, and repeated trials running

Fig. 7c – Image of a 3D printed scleral cover shell prosthesis using polylactic acid (PLA). Permission granted from Fig. 5 of.[66]

the risk of discomfort, corneal epitheliopathy or infection. Recently, 3D printing has been used to print the cornea for use in simulated fitting of RGCPLs (Fig. 9).[32, 80] In this hypothesis testing study, the corneal anterior surface data of 1 myope and 1 keratoconus patient were collected by topography scanning, and an equal-scale solid model of the cornea was made by 3D printing. The patient-specific model was used for RGPCL trial until a satisfactory fitting on the model and then fitted to the patient and compared with traditional fitting. In keratoconus, the number of try-ons was reduced using the 3D printed cornea (twice), compared with that of traditional method (5 times). In high myopia, the lenses were fitted in 1 try-on either by the traditional method or the 3D printed model method.[79]

This model could be developed further by adding an adjustable eyelid to the 3D printed model, as well as simulating a tear film to mimic the influence of the normal anatomical environment. Development of the optimal biomaterial for the model to better resemble human cornea would also be beneficial.

2.1.3. Surgery

2.1.3.1. Surgical planning The advantages of applying 3D printing to surgical planning have been widely demonstrated across various surgical specialties, such as spinal surgery, neurosurgery, visceral surgery, cardiovascular surgery, and plastic surgery.[11, 16, 21, 30, 58, 78] In ophthalmic practice, surgical planning includes visualization of patients' anatomy, simulation of operative procedures, and preparation of surgical devices and instruments. Previous studies have suggested the role of 3D printing in some complicated cases such as orbital reconstruction surgery (Fig. 10), which remains a great challenge for ophthalmologists because of the complicated anatomy of the orbit and the restricted operative area. Specifically, 3D printing can help surgeons to better shape the implanted device to fit the orbit floor contours[36] and define the orbital fracture area.[16] With the aid of 3D printing, surgeons can vividly simulate specific operations on patient-specific models, to improve the clinical outcomes of surgical treatments.

2.1.3.2. Surgical instruments Apart from preoperative planning, 3D printing has been employed in manufacturing customized surgical instruments that can better meet the personal demands of surgeons, such as dominant hand and size. For example, surgeons are provided with different sizes of gloves but only a single size of surgical instrument. In this case, 3D printing can be used to produce customized instruments to meet individual needs. Compared with the conventional manufacture of surgical instruments, 3D printed instruments are produced with the overall cost and production time reduced. For instance, a basic operation kit for performing laparotomy, ligation, and splenectomy on a surgical simulator, including forceps, hemostats, and needles, can be printed in 6 hours using FDM technique.[35]

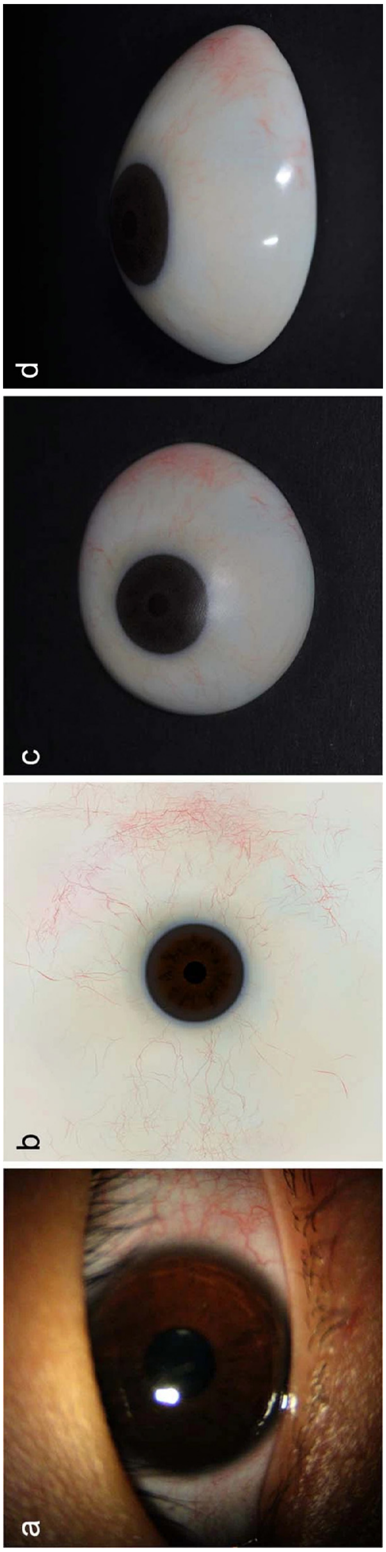


Fig. 7d – Images of eye and 3D printed ocular prostheses. Permission granted from Figs. 4A, 4B, 5 of.[32]

2.1.4. *Medical education*

2.1.4.1. *Anatomical models* Owing to the detailed and complex structure of the eye as well as variations in anatomy, current radiographic images can fail to yield sufficient information for teaching trainee ophthalmologists. With the emergence of 3D printed anatomical models, it is possible to recreate the detailed structure of the eye and therefore enhance the education of medical students and trainee ophthalmologists.

One example of anatomy that is difficult to teach is the orbit, which is considered to be one of the most complicated anatomical regions in the human body, as well as having a high rate of variation.[63] Currently, 3D printed models of the orbit containing both bony structure and soft tissue can provide visual details of ocular anatomy that have been previously reported to help improve the learning experience and overall outcomes, compared with the traditional textbook-based and computer-based learning modalities.[27, 42, 60] Moreover, given the shortage and ethical issues surrounding traditional cadaveric models, 3D printed models are currently considered a promising alternative due to high precision, reduced cost and reproducibility, especially for cases with rare diseases and complicated conditions.[2, 70] In addition, patient-specific anatomical models can enhance the surgeon's preparation and the patients' confidence in their surgical team. By demonstrating the pathological condition and surgical procedures on realistic models, patients and their families can better understand their own conditions.[8, 41]

2.1.4.2. *Surgical simulator* Similar to 3D printed models for preoperative planning, 3D printed surgical simulators provide visualised surgical training, such as orbital surgery and keratoplasty, which can help improve confidence during the actual operations. In 2019, an innovative experimental model was developed to allow the simulation of the Descemet membrane endothelial keratoplasty (DMEK).[15] In this study, human donor corneas were mounted on artificial anterior chamber with 3D printed iris, which also allowed the adjustment of pupil size and anterior chamber depth and thereby better mimicked the real situation.

The next development steps have an opportunity to augment the learning experience by developing 3D printed models with enhanced functions and simulators of different types of ophthalmic surgery, such as phacoemulsification and trabeculectomy. Currently, materials used in FDM, SLS and SLA are generally too hard or brittle for dissection exercises, so the development of materials to allow more realistic surgical simulation will be crucial.

2.2. *Quality assurance of 3D printed models*

Quality assurance (QA) is a series of error prevention means to provide sufficient confidence for a product through systematic measurement and processes monitoring. It has been developed to ensure the quality of medical treatments for decades. With the increasing popularity of medical 3D printing, there is growing demand for extending quality assurance and control to 3D printed devices. In general, model quality is evaluated by measuring the degree of reliability, maintainability, and sustainability. Researchers assessed the accuracy of 3D printed models using different measuring methods including

Fig. 8 – Image of a 3D printed prosthetic eye. Image of a fully 3D printed prosthetic eye under an eyelid mount. Courtesy of G. Bott and S. Bell, Ocupeye Ltd, UK.

(1) physical measurements; (2) digital photographic measurements; (3) 3D surface scanning; (4) photogrammetry and (5) CT scans.[56] Given the advantages and disadvantages of these measurement methods (Table 8), different products could be evaluated by the most suitable means. In this study, the importance of monitoring the entire production process was to minimize errors and improve the quality of 3D printed models and move to establish a validated verification system for the quality assurance of 3D printed ophthalmic models before their wider applications commence in ophthalmology.

2.3. *Challenges of 3D printing in ophthalmology*

Despite the potential successes of 3D printing in ophthalmic practice, some limitations of this emerging technology must be addressed so that adoption and wider applications in ophthalmology can be realized.

2.3.1. *Quality of 3D printed models*

In general, the quality of a model can be assessed in terms of accuracy, durability, and user satisfaction. For accuracy and durability, impact factors generally include medical images of patients, types of 3D printer, printing parameters, and the properties of raw material. For example, if the segmentation process of 3D printing is performed manually, the proficiency of technicians may affect the reliability of the 3D printed product. Furthermore, some anatomical structures such as the choriocapillaris cannot be 3D printed accurately as current imaging technology cannot capture the details of the vessels.

With regard to 3D printers, models printed by FDM are relatively cost-effective, but exhibit lower resolution and more surface roughness. Compared with SLS and SLA that only produce unicolor models, MJM can produce multi-color models and simulate the texture of both hard and soft tissues using different biomaterials.

The selection of biomaterials is important in deciding how best to create a 3D- printed object in different ophthalmic cases. For example, biomaterials used for 3D printed orbital models should possess prolonged biodegradation rate and higher mechanical strength, which therefore explains the use of metals, ceramics, hard polymers, and composites for the bony structures of orbital models. In contrast, for 3D printed visceral organs selected biomaterials such as soft polymers should have higher degradation rate and flexibility. Conversely, some users of 3D printed products were not satisfied with the 3D printed models because of their shortcomings.[10, 14, 45]

Table 8 – Advantages and disadvantages of five measuring methods of model verification. Adapted from Table 3 of[56].

Measuring Methods	Advantages	Disadvantages
Physical measurements	①Cost-effective ②Straightforward	①Difficult to measure internal structures ②Non-linear models cannot be measured
Digital photographic measurements	①Cost-effective ②Non-linear models can be measure by calipers ③Simple set-up	①Errors can be caused by different illumination ②Interested features must be on the same plane as the reference feature and scale
3D surface scanning	①High resolution ②Portable	①Expensive ($1,000-$1 million) ②May not be easy to scan the reflective model surfaces
Photogrammetry	①Cost-effective	①Requires the knowledge or image processing principles and software
CT scanning	①Fast ②Can measure the internal geometry of models	①Expensive ②Requires original DICOM image registration.

DICOM = Digital Imaging and Communications in Medicine.

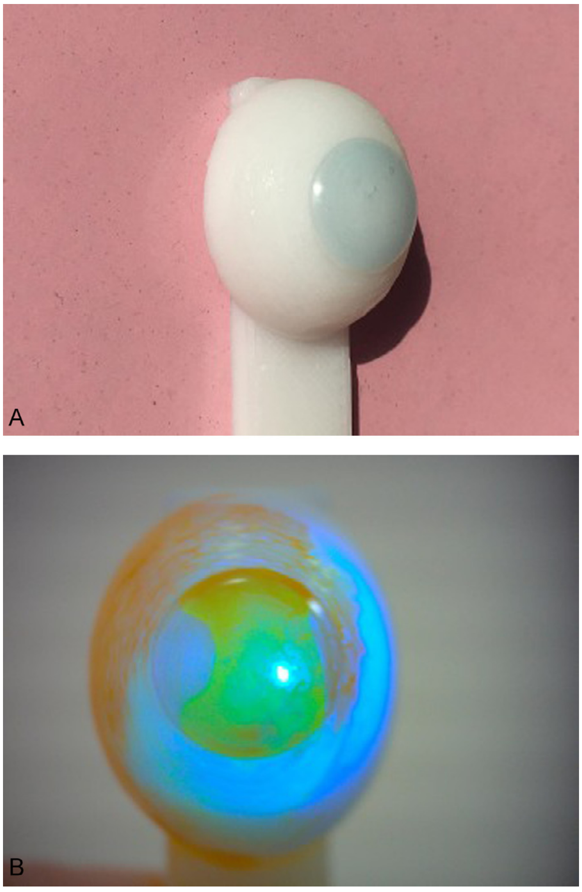


Fig. 9 – Images of 3D printed contact lenses Fig. 9A: 3D printed corneal model for RGPCL try-on. Fig. 9B: Simulation of astigmatism fitting. Permissions granted from Fig. 2-3 of.[80]

2.3.2. *The similarity of 3D-printed models and native tissue*

The similarity of 3D printed models and native tissue is generally defined as the precision of the products, which can be assessed according to structure, size, function, and simulation of the surrounding environment; however, the similarity of most of the 3D printed models and their native tissue in previous studies is not well-aligned. For instance, the surgical simulator of orbital surgery was fabricated without surrounding structures of the globe such as the extraocular muscles. In another use, the viability of cells in 3D printed implant such as retina remains uncertain.[69] In addition, the technical resolution of current 3D printers restricts the dimension of the components of 3D-printed objects, such that microscopic structures such as capillaries, cannot be printed precisely to mimic the native vessels.

2.3.3. *Time*

One of the limitations of 3D printing is the variable time required to produce 3D models depending on complexity, including the time for the acquisition of medical images to further processing of digital models and printing. As described above, it can take hours or even days to produce a 3D-printed product. Although 3D printing has been regarded as an alternative manufacturing method that can be performed at any place, it is still challenging to create 3D printed models in emergency cases.[6] In such urgent situations, 3D printing as it is currently available may take too long to produce customised surgical implants for intraoperative use.

Although 3D printing may shorten surgical time by use of customized anatomical models, their planning and production is currently time consuming.[36, 61] Hence, complicated elective surgical cases will not begin to benefit from this technology until time frames and costs start to reduce significantly. 3D printing of prosthetics may however be quicker than traditional artisan manufacture. The latter is a handmade process, with many man-hours of artistry to manufacture a bespoke product. 3D printing has the potential to change this to a fraction of the time taken, with potential of better mimicry of the eye's normal anatomy and patient acceptance.

2.3.4. *Cost*

Compared with conventional production, the current relatively high cost for 3D- printed medical devices remains a limiting factor of its use, which is generally determined by the

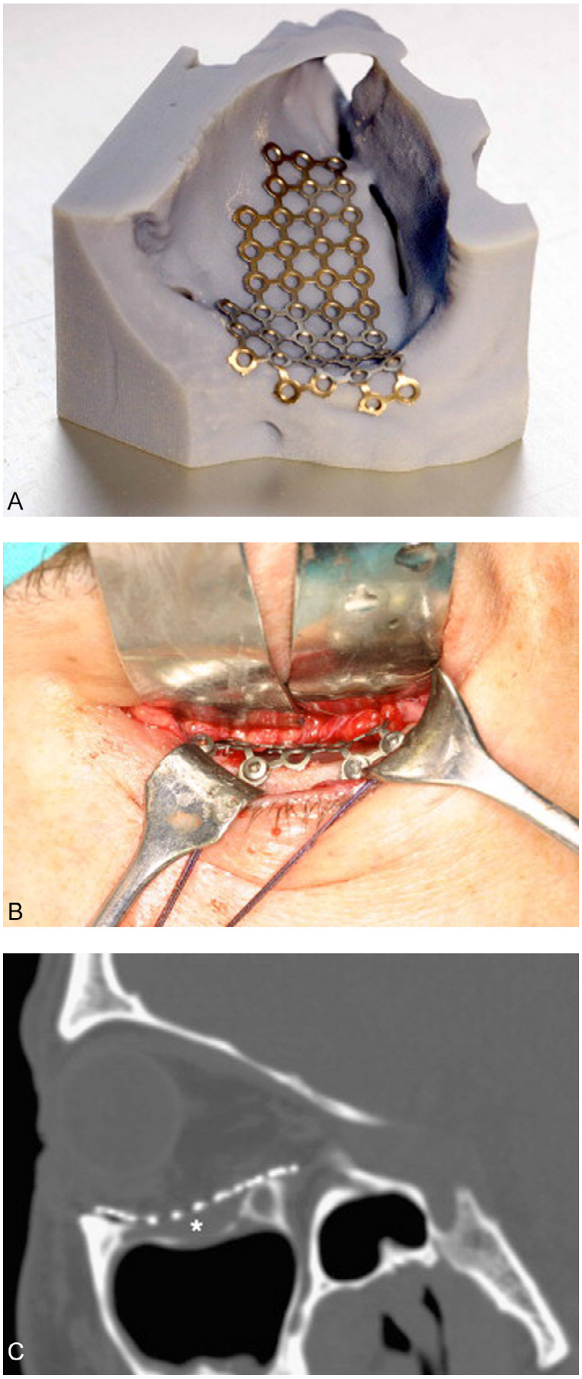


Fig. 10 – Images of the use of 3D printing in orbital reconstruction surgery Fig. 10A: Image of using a 3D printed left orbital floor model to shape a titanium mesh before the surgery. Fig. 10B: Left orbital floor reconstructed by pre-shaped titanium implant. Fig. 10C: CT image of the left orbit after reconstruction surgery showing the restored orbital volume of patient's reconstructed left orbital floor. Permission granted from Fig. 5-7 of.[36]

design, type of 3D printer, size of the desired model, raw materials and related patents.[31]

The cost-effectiveness of 3D printing is controversial, though with early patents expiring, the costs are anticipated to fall. In general, the clinical outcomes between 3D-printed models and conventional medical devices or surgery is similar.[12] As a result, doctors and patients may show little interest in adopting new technology; however, cost gains could be made in better surgical planning and treatment, reduced time of operation and complications to compensate for the additional cost of 3D printing in complicated cases.[6]

In terms of prosthetic devices, a one-off cost can be affordable for many patients, but there is a lifetime financial burden especially for those who need frequent repair and replacement.[10] A conventional artificial eye costs approximately US$1800, but some 3D-printed models may cost 40 times less[F,I]. Though such technology may replace handmade manufacture, the skills of the ocularist will still be needed to fit the prosthesis to the patient.

2.3.5. *Ethical challenges*

With the development of 3D printing, ethical concerns have been raised about the commercialization of human organs, similar to cloning technology. There have even been some religious objections to the technology.[49] For example, it is debatable whether 3D printers can be used to print a mutated organ capable of longevity. Some are also concerned that this technology is for only for the wealthy, raising the possibility that disparity in healthcare may be widened, especially if objects that are 3D printed are commercialized at high cost.

Another ethical issue centers on intellectual property. The domains of intellectual property are copyright (unregistered right to protect artistic or creative works), design protection (protects the distinctive shape and appearance of objects and can be registered or unregistered), patent (registered right that protects novelty or innovations), and trademark (protects the originator of goods). In England, 3D-printed models for non-commercial personal use do not contravene patent protection law, which therefore allows the individual to produce 3D-printed products anywhere as long as they have relevant digital files and 3D printers.[9] Since people can currently download copyrighted files such as movies and music online, it is not inconceivable that individuals will be able to download the information and instructions of certain objects and reproduce them easily by 3D printing. Besides, objects can be scanned and reproduced by 3D printing without requiring the original commercial digital files, which raises a concern about whether these 3D printed products infringe upon the intellectual right of the original companies.[54]

2.3.6. *Legal challenges*

Although 3D printing technology has been available for decades, the regulation of 3D printing is still not complete. In the US, the application guidelines for 3D printing were published by the FDA in 2017[O]; however, there is still no legal regulation specifically for this technology, nor clarity on to whom the legal responsibility of 3D printed products falls. As 3D printers and printable materials become more and more accessible, it will be possible for healthcare providers, researchers, and individuals to manufacture customized products using 3D printing techniques, which therefore contributes to the varying quality of 3D-printed products and the generation of related safety issues. Because of the undefined legal responsibility of current 3D-printed products, it is challenging to process litigation and liability claims regarding the occurrence of medical complications related to the use of 3D printed models. Therefore, further efforts will need to be made to establish legal provisions regarding 3D printing before its wider applications in ophthalmology, especially in terms of patient safety.

2.3.7. *Standardization of 3D printing*

A 3D-printed product is produced through image acquisition, image post-processing and rapid prototyping; each process plays an important role in the quality of the final product. Currently, there is no consensus on the standard of 3D-printed products, limiting the generalizability of the process. In order to improve the quality and consistency the 3D printed product, a standard operating protocol (SOP) for medical uses is necessary and would best written by experts who have multidisciplinary knowledge of the 3D printing process chain. The SOP should include (1) image acquisition protocol for 3D modelling; (2) image post-processing protocol for generating medical images to 3D model; (3) product manufacture protocol for 3D printing techniques, that is, which printer(s) should be used for a specific product; (4) quality assessment to ensure the safety of 3D printed product for medical use.

2.4. *Future work*

2.4.1. *Investigations of appropriate biomaterials*

In orthopedics and dentistry, metal, metal alloys, and ceramics are routinely used for implants, while composites are normally used for prostheses and tissue scaffolds (Table 2). In ophthalmology, further research is needed to develop natural biomaterials and thereby improve the biocompatibility of biomaterials. Such safety studies will need to avoid the host's immune response, while further advancement of material properties such as transparency, mouldability, and durability will improve the performance of 3D printed ophthalmic models. Besides, future comparative analysis and in vivo studies should be performed to identify the optimal biomaterials for printing different ocular structures such as uveal tract and sclera.

2.4.2. *Improvement of the quality of 3D-printed products*

To expand the applications of 3D printing in ophthalmology, quality improvement in a defined way will be necessary. This will need to consider precision, accuracy, biocompatibility, and nontoxicity.[29, 44, 73]

Moreover, similar to the National Joint Registry in the United Kingdom, a clinical registry system of 3D printed products could be built by each nation to develop a database of the use of 3D printing in the medical field, which allows researchers and clinicians to conduct comparative analysis of the performance of different 3D-printed products and identify the need of modification, reporting of adverse effects and licensing of products for human use.

2.4.3. *Long-term outcomes of 3D-printed products*

Although 3D printing has been successfully applied in manufacturing various products, the long-term outcomes of 3D-printed products are yet to be assessed, as limited clinical trials have been done in this area. In general, long-term outcomes of 3D printed products can be divided into two main aspects: clinical and patient outcomes. In terms of the clinical outcomes, clinical efficacy and safety of 3D printed products should be further evaluated. It is of great importance to assess the incidence of complications such as infections, localized, and systemic immune reactions and implant failures in patients receiving 3D printed products. In terms of the patient outcomes, future studies can assess the satisfaction and quality of life in patients treated with 3D-printed products.

2.4.4. *Integration of 3D scanner and 3D printer*

The current production process of 3D printing includes image acquisition, postprocessing, and rapid prototyping. As with all-in-one home inkjet printer, where one machine contains the functions of scanning, printing and copying there is the possibility of combining 3D scanner and 3D printer into single machine. This would require a smaller footprint and be more cost-effective in driving this technology forward.

2.4.5. *Generalizability of 3D printing*

The generalizability of 3D printing is promising, but limited by many factors. These include the cost of setting up a new process for a product, research on compatibility of biomaterials, acceptability of physicians and their patients, regulatory, ethical, and legal hurdles, as well as standardization and regulation of this industry. More support from government, industry, healthcare, and university sectors is necessary to develop, scrutinize, and promote the benefits of this technology. Regulation to standardize, validate, and monitor the manufacture of 3D printing falls on government to protect the rights and interests of different stakeholders, including image creator, product producer, product user, and ultimately the patient. Support for applied research would also be welcome, in innovative ways such as subsidizing technology companies for equipment purchase and talent recruitment. Universities and technological institutes could partner with enterprise companies not only for research but also to introduce 3D printing to new generations of students at an early stage of their careers.

2.5. *Limitations of this review*

We included only English literature searches and references in this review. The search terms include the synonyms of 3D printing, ophthalmology, possible applications of 3D printing in healthcare and several medical specialties. As a result, selection and language biases are considered a potential confounding factor in this review. The available evidence for 3D printing in ophthalmology is limited in the published literature and governmental guidelines, so some information about ongoing studies is referenced to commercial websites and news sources and hence may suffer from lack of robust peer review found in scientific publications. Lastly, it must be noted that most included 3D printing publications are of studies still in an experimental or development stage, which may lag behind new innovations in clinical practice.

3. Conclusion

As an emerging technology, 3D printing allows the customization and fabrication of 3D objects using a "layer upon layer" method. Since the introduction of 3D printing, it has been rapidly developed and increasingly applied in the medical field, including dentistry, orthopedics, and head and neck surgery. Although the role of 3D printing in ophthalmology is still not fully understood, nor yet fully realized, previous studies have suggested the potential applications of 3D printed objects in ophthalmic practice, including diagnostic methods, clinical devices, surgical treatment, and medical education.

Given the challenges of this emerging technology in ophthalmology, further studies are required to improve the performance of currently used biomaterials and increase the accuracy of 3D printing devices. Future development of bioinks will also be of great benefit to 3D bioprinting of ophthalmic structures. Finally, future use of 3D printing will require further quality verification of 3D printed ophthalmic models, ensuring cost-effectiveness, time efficiency, and resolving legal and ethical issues.

4. Method of literature search

4.1. *Databases, search engines and internet search*

To review the concepts and applications of 3D printing, especially in ophthalmology, we searched two retrieval databases and several websites. The Ovid Medline 1946 – July 2019 and Ovid Embase 1947 – July 2019 databases were searched and an internet search was conducted on the following websites: (1) The U.S. Food and Drugs Administration (FDA); (2) www.3dprint.com; (3) https://3dinsider.com/; (4) www.3ders.org. The websites of the FDA provide information about approved clinical devices such as implants and instruments in ophthalmology as well as other specialities. The third, fourth, and fifth websites contained the latest information in 3D printing.

4.2. *Search keywords*

In order to acquire adequate literature and information, the topic of this article was cut down into two separate keywords, "3D printing," and "ophthalmology," and their synonyms. Medical Subject Headings and Free Text Terms were used to search for the concepts. Boolean Operators "OR" and "AND" were applied to merge search lines. Four groups of keywords were searched in the databases and search engine. The first group was the terms referring to 3D printing: 3D and print* or 3D print* or 3 dimension* print* or three dimension* print* or three D print* or rapid prototype* or layer* manufactur* or additive manufactur*. The second group was the terms related to ophthalmology: ophthalm* or ocular or cornea* or retin* or scler* or vitre* or iris or pupil or orbit* or choroid*; the term eye* is excluded as it is too broad. The third group was the terms included the possible applications of 3D printing in healthcare: surg* or implant* or prosthe* or anatom*. The fourth group was the terms of several medical specialities in order to obtain additional information of 3D printing in other disciplines: dentis* or orthopedics or otolaryngology or otology or head and neck surg* or cadi* or plastic or gastrointestinal*. The keywords of the first and second group were combined to obtain the results of 3D printing in ophthalmology. Then the first, second and third group were combined to obtain the search result of the possible applications of 3D printing in ophthalmology. Finally, the first and third group, the first and fourth, and the first, third and fourth group were combined respectively to receive results of the application of 3D printing in other specialities.

4.3. *Inclusion and exclusion criteria*

Literature that met the following conditions was reviewed: (1) The abstracts or whole papers written in English were included. Non-English articles were excluded. (2) The basic principle, development and applications of 3D printing or rapid prototyping or layered manufacturing or additive manufacturing were explained. (3) The applications of 3D printing in the medical field were illustrated, such as diagnosis, various clinical devices such as implants and prostheses, drugs, surgery and education. (4) Applications of 3D printing in other medical disciplines. The title or abstract of publications with any one of (2), (3), (4) were considered. No limitation was applied with regard to the year of publication.

5. Disclosure

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