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REVIEW ARTICLE

Implementations of 3D printing in ophthalmology

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Abstract

Purpose The purpose of this paper is to provide an in-depth understanding of how to best utilize 3D printing in medicine, and more particularly in ophthalmology in order to enhance the clinicians' ability to provide out-of-the-box solutions for unusual challenges that require patient personalization. In this review, we discuss the main applications of 3D printing for diseases of the anterior and posterior segments of the eye and discuss their current status and implementation. We aim to raise awareness among ophthalmologists and report current and future developments.

Methods A computerized search from inception up to 2018 of the online electronic database PubMed was performed, using the following search strings: "3D," "printing," "ophthalmology," and "bioprinting." Additional data was extracted from relevant websites. The reference list in each relevant article was analyzed for additional relevant publications.

Results 3D printing first appeared three decades ago. Nevertheless, the implementation and utilization of this technology in healthcare became prominent only in the last 5 years. 3D printing applications in ophthalmology are vast, including organ fabrication, medical devices, production of customized prosthetics, patient-tailored implants, and production of anatomical models for surgical planning and educational purposes.

Conclusions The potential applications of 3D printing in ophthalmology are extensive. 3D printing enables cost-effective design and production of instruments that aid in early detection of common ocular conditions, diagnostic and therapeutic devices built specifically for individual patients, 3D-printed contact lenses and intraocular implants, models that assist in surgery planning and improve patient and medical staff education, and more. Advances in bioprinting appears to be the future of 3D printing in healthcare in general, and in ophthalmology in particular, with the emerging possibility of printing viable tissues and ultimately the creation of a functioning cornea, and later retina. It is expected that the various applications of 3D printing in ophthalmology will become part of mainstream medicine.

Keywords 3D printing · Bioprinting · Ophthalmology · Cornea · Retina

Introduction

3D printing

Three-dimensional (3D) printing is an all-inclusive term for a variety of methods that use digital data to produce 3D objects made of various materials (both synthetic and organic). 3D printing is also referred to as "additive manufacturing" due to the process of depositing layer after layer of material until the desired object is constructed. This technology will likely become a "disruptive technology," defined as a change that significantly affects the way and entire field functions [1]. The origin of 3D printing began in the early 1980s when Hideo Kodama invented an automatic method for fabricating 3D plastic models with a photo-hardening polymer at the Nagoya Municipal Industrial Research Institute [2]. It was not until 1984 that three French inventors, Alain Le Méhauté, Olivier de Witte, and Jean Claude André, conceived the idea and filed a patent for a stereolithography (SLA) process [3], which is a method for 3D printing that produces objects through photopolymerization, a process by which light causes molecules to adhere and form polymers. Unfortunately, their patent application was abandoned by the French General Electric Company and French laser and optics company CILAS, due to a perceived lack of business potential [4]. Three weeks later, an American inventor, Chuck Hull, filed

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a patent for the process and consequently was granted the official title "inventor of stereolithography." This rapid prototyping technology was later utilized in the 3D printing industry [4, 5]. The term "3D printing" was coined in 1995 by Prof. Emanuel Sachs at Massachusetts Institute of Technology (MIT) [6]. Currently, various 3D printing methods exist, with printers spanning the \$99–\$2,500,000 USD price range, with a typical resolution of 100 μm per layer and nozzle diameter of 0.4 mm. Smaller nozzles not only produce higher resolution prints, but also inversely increase printing time. The main difference between the processes is the way layers are deposited on each other during production, as well as the choice of printing materials used. Two main methods include the following: (1) Extrusion: a process in which melted material is pushed through the nozzle, and (2) Sintering: a process in which a powder or liquid is deposited one layer at a time; then light is applied to harden the powder. Each of these two methods has advantages and disadvantages which lay beyond the scope of this review. The production of a 3D model may take minutes to several days, depending on the size, resolution, choice of material, choice of printing method, the printer used, and complexity of the model [7]. Nevertheless, regardless of the printing method chosen, they all provide quick prototyping as compared to the pre-3D era. Consequently, 3D printing significantly speeds up the design cycle as well as reducing costs of both the development as well as the manufacturing process in a variety of industries, healthcare being one of the more challenging, yet rewarding.

Search and study selection criteria

We reviewed publications inspecting the implementation of 3D printing in healthcare in general, and in ophthalmology in particular. A computerized search from inception up to 2018 of the online electronic database PubMed, was performed, using the following search strings: "3D," "printing," "ophthalmology," and "bioprinting." Eligibility of the studies was initially verified by excluding non-relevant studies after manually examining the titles and/or abstracts. Additional data was extracted from relevant websites. No limitation was applied regarding the year of publication. Articles in non-English languages were excluded if no English translation was available. The reference list in each relevant article was analyzed for additional relevant publications.

3D printing in medicine

The ability to rapidly produce custom objects for a fraction of the price of conventional prototyping and production hastened the implementation of 3D printing in the healthcare system. In 1990, the first anatomical model produced by 3D printing was presented at the University of California by Mankovich et al. The model depicted in detail the cranial bony anatomy, derived from a CT scan, illustrating internal anatomical details, including sinuses and foramen. Production of the model took 16 h using the stereolithography process [8]. In 1998, an anatomical model used for bone reconstructive surgery was the first 3D printing application applied for surgical planning, and the harbinger of future production of personalized implants [9]. Since then, successful applications of personalized printed models were initiated in a variety of medical fields, such as in neurosurgery [10], otorhinolaryngology [11], cardiology [12], pulmonology [13], general surgery [14], and orthopedic surgery [15, 16] to name a few. These models provide a 3D surgeon's view of the anatomic relationship between the operated organ and surrounding structures. While 3D printing in medicine began with the creation of models for surgical planning and education purposes in the mid-1990s, it took nearly two decades to expand into printing custom-made implants with exact specifications that could be implanted into the human body. The first examples of implantable devices included the following: (1) A bioresorbable 3D-printed airway splint for infants with severe tracheobronchomalacia was introduced in 2013. The splint was positioned around the infant's airway to support it and prevent unwanted airway collapse, allowing expansion with growth [17]. (2) In 2014, a team of surgeons from Peking University Third Hospital, Beijing, conducted the first surgery, inserting a titanium, 3D-printed vertebrae in a 12-year-old boy [18]. A major advancement in the evolution of 3D printing in healthcare was the introduction of "bioprinting" or "organ printing." It is a process in which layers of living differentiated cells (or stem cells) and growth factors are deposited onto synthetic "scaffolds" (i.e., composed of a gel medium or sugar matrix) forming a 3D living structure that contains basic vascular structures that are themselves capable of generating additional tissues and organs presenting natural tissue characteristics, thus supporting the adhesion, proliferation, and differentiation of living cells. The deposited material is usually referred to as "bioink." In 2006, scientists at the Wake Forest Institute for Regenerative Medicine, USA, produced the first 3D-printed lab-grown organ that was later implanted in a human. Seven candidates for cystoplasty, aged 4–19 years, were selected for transplantation. Autologous urothelial and muscle cells were grown in culture and seeded on a bladder-shaped collagen composite scaffold [19]. This was made possible following work performed at the institute starting as early as 1999 [20]. Biomedical templates for cell culturing (also called scaffolds and biomaterials) can alternatively be created from microstructures with a 3D internal geometry and controllable porosity. The fused filament fabrication process using polylactic acid (PLA) is commonly used for creating such templates [21]. Common biomaterials in use include tissue-specific decellularized extracellular matrix, poloxamers, and alginate/gelatin/collagen/hyaluronic acid–based materials. Each of these biomaterials exhibits unique printability properties such as viscosity, cross-linking properties, incorporation of minerals and ions, and post-printing manipulation. A main printing approach would be to print a scaffold through extrusion and then populate the scaffold with living cells. As mentioned before, a novel application of bioprinting is the production of regenerated bone and cartilage, personally tailored for various orthopedic conditions [22].

Despite impressive progress in the field, the printing of fully functional organs is still not possible, mainly due to the lack of successful implementation of crucial elements such as vasculature, secretion tubules and ducts, and other central factors necessary for the viability and stability of a living organ.

3D printing in ophthalmology

3D printing applications in ophthalmology are not conceptually different from those in other fields of medicine. Nevertheless, the accessibility of the inner eye and particularly the anterior segment, coupled with the immune privileged status of the eye, and the multitude of tools available for diagnosing and identifying various ocular conditions, turn the eye into a fertile ground for the implementation of 3D novel printing solutions. Advancements in biocompatible materials and the use of autologous stem cells enhance implant adaptability and reduce the risk of rejection as well as irritation caused by the implanted material. 3D printing milestones, from inception to the present, with an emphasis on healthcare achievements and applications, are depicted in Fig. 1. The following is a summary of the main applications of 3D printing in ophthalmology.

Anterior segment

Cornea

The cornea is the most frequently transplanted organ in the USA, with over 40,000 cases performed annually [23]. Yet, according to a global survey published in 2016, 53% of the world's population lack accessibility to this sight-restoring procedure [24]. Additionally, patients may suffer an immune rejection to the transplanted allogeneic graft even years following the procedure. The cornea possesses a number of "printing advantages" over other tissues in that it is relatively homogeneous at the cellular level, has an extremely low metabolic demand, and is entirely avascular. 3D printing is a potential solution that can alleviate the shortage of donor tissue and answer the problem of implant rejection. As recently published by Isaacson et al., an artificial cornea that was made from a combination of alginate, collagen, and human stem cells made to differentiate into corneal stromal cells was successfully printed at Newcastle University [25]. A gel-like mix can be extruded from an off-the-shelf 3D printer into the shape of a cornea in a matter of minutes. Moreover, the printed cornea is designed to match a particular patient's unique geometrical and thickness specifications. Nonetheless, clinical trials are needed before establishing safety and determining long-term success. Scientists from all over the world are participating in the race towards mass production of an artificial cornea. In 2017, a team of Spanish researchers, headed by de Miguel MP at the Spanish Institute for Biomedical Research, La Paz Hospital, Madrid, announced their intention to create a transplantable cornea using 3D bioprinting with a forecast of widely implementing it for human use by 2022 [26]. Once this technique matures, it is anticipated that a 3D-printed cornea, specifically tailored to the patient's anatomy, specifications, and needs, will be printable within five working days. The process is based on the synthesis of a polymeric extracellular matrix of collagen that mimics the human cornea with stem cells printed into the matrix. The challenge of assuring corneal

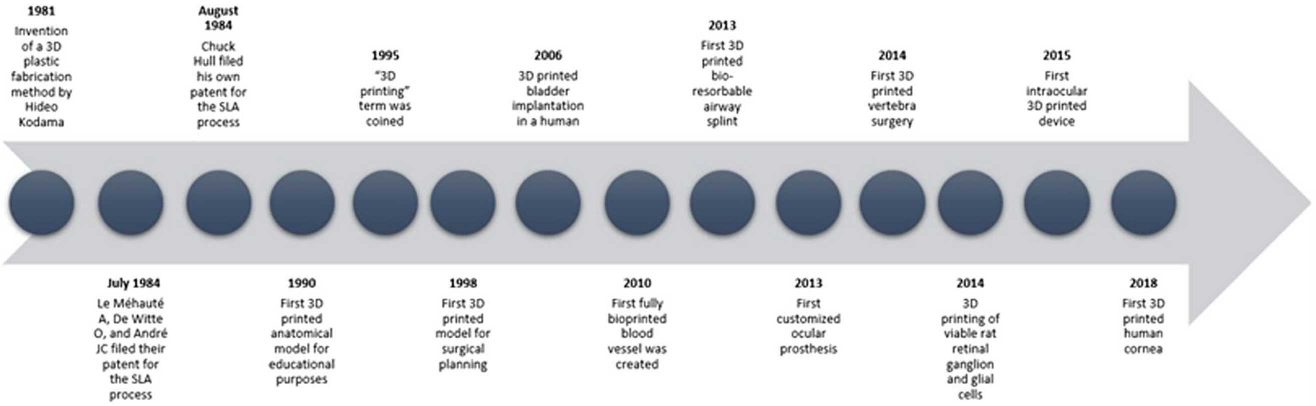

Fig. 1 Milestones in 3D printing, from inception to the present, with an emphasis on healthcare applications

transparency may be addressed by designing parallel collagen fibers printed with pre-defined specific distances between them, imitating the 3D structure of the original human tissue.

A fish scale–sourced scaffold for artificial corneal printing has been suggested by Potgieter et al. from Massey University of New Zealand. This team is investigating the printing of an artificial cornea from collagen extracted from the scales of the Hoki fish, a specimen found in abundance off the coast of New Zealand that, according to their findings, was shown to be tolerated by the human body immune system [27]. The team created a successful prototype device and hope that mass production will be ready for testing by the end of 2018. 3D printing in corneal tissue engineering and regenerative medicine is by far the most advanced in ophthalmology. In their review, Gibney et al. discuss different approaches for corneal substitute production and describe a unique method for producing thin collagen films which are suitable for culturing corneal mesenchymal stem cells, all made with 3D printing [28]. Due to their susceptibility to environmental factors, extraction and culturing of living cells pose a challenge for mass production of 3D-printed corneas. Recently, Biazar et al. reviewed potential materials for utilization of 3D printing in personalized production of synthetic corneas without the use of living cells [29]. In a 2016 analysis by Kai-Ling et al., three methods for preparing donor corneal grafts for keratoplasty in Singapore were compared, demonstrating the cornea cost, excluding other procedural costs, to be $3000 USD. The cost of the most commonly used synthetic cornea, the Boston Keratoprosthesis (KPro), was estimated at $5000 USD as of 2010 [30]. Polymethyl methacrylate (PMMA) filaments are widely used in the 3D printing industry for producing rigid, light, transparent customized objects, such as aquariums and other translucent and transparent containers. The Auro Kpro, an Indian low-cost alternative keratoprosthesis, comprises of a back plate made of PMMA instead of Boston KPro's titanium back plate, is estimated at a mere $100 USD per unit. Moreover, it maintains comparable visual outcomes, postoperative complication rate, and retention rates [31]. The Auro Kpro is an example of how 3D printing can be utilized to create a cost-effective alternative to a more costly product. To maintain 3D printing, as a feasible and widely available solution for artificial cornea production, scientists and engineers need to constantly seek components that can be replaced by low-cost printed substitutes, as demonstrated by the Auro Kpro example.

Lens surgery

3D printing of an intraocular lens (IOL) presents several obstacles yet to be overcome. The refractive index (RI) of a material describes how fast light travels through the material. It is defined as $n = \frac{c}{v}$ and stands for 1, 1.376, and 1.336 for air, tear film, and aqueous humor, respectively. To focus light, the RI of the lens should exceed that of the aqueous humor, and it varies from 1.38 near its surface to 1.409 in its center [32]. Further optical characteristics of the human lens are thoroughly described in various studies [32–34]. Today PMMA-like filaments are not capable of producing flexible objects, therefore limiting its use in creating foldable artificial IOLs. Recent studies highlight the possibility of using translucent soft materials such as silicone for creating 3D-printed foldable IOLs [35]. To effectively mimic the IOL's optical characteristics, printed material should also take into consideration the different RI among the printed layers, a feature that currently is not yet precise enough. In 2016, Debellemanière et al. presented a 3D-printed reproduction of the Ridley lens. The lens was made of a PMMA-like photopolymer material. Although this lens design is mainly of historical value, this bi-convex lens demonstrated acceptable transparency (an average of 75% light transmission in the visible spectrum) [35].

The first intraocular device designed and manufactured using 3D printing was a 3D pupil expansion device presented by Canabrava et al. in 2015, named “Cana's Ring.” The device secures the pupillary edge of the iris during cataract extraction, providing pupil dilation of 6.5 mm, utilized in cases with floppy iris syndrome (IFIS) and non-dilatable pupils [36].

Posterior segment

Retina

3D printing may be used for enhancing current retinal imaging techniques and improve the visualization of optical coherence tomography (OCT) images. Although the retina is a 3D structure, ophthalmologists currently view 2D images from fundus photography and OCT images for in-depth analysis. 3D-printed retinal model may provide additional information for both the physician and patient, with a better grasp of the anatomy and pathology of lesions and surrounding tissues. 3D-printed models can be used for educational purposes and to enhance a trainee's perspective by correlating 2D imaging with 3D models. Choi et al. demonstrated that 3D-printed models may provide accurate preoperative information regarding the surface and shape of an epiretinal membrane, including subtle vitreoretinal tractions and adhesion points. This custom-made individualized printed model, based on the OCT scan, assisted in determining the starting point of epiretinal membrane peeling during vitrectomy [37]. 3D printing of optical coherence tomography angiography (OCTA) scans, intended to achieve enhanced resolution and speckle-free visualization of retinal and choroidal vasculature and choroidal tumors, were recently demonstrated by Maloca et al. Raw OCTA data was processed to obtain a printable 3D version that depicted the 3D arrangement of the vasculature along the inner retinal surface with vertical branches connecting to deeper retinal vascular networks [38, 39]. A 2016 review by Lorber et al. listed the necessary steps towards the creation of a functional printed retina. Towards this goal, it has been demonstrated that rat retinal ganglion cells and glial cells can be successfully printed using a piezoelectric inkjet printer without loss of viability and certain phenotypic features [40]. Further research will determine if these findings can be translated to other retinal cell types. Should this be achieved, the possibility of printing multiple cellular layers and ultimately creating an entire retina could be entertained, at least be theoretically.

Additional applications and accessories

3D printing can assist in the design and manufacturing process of ocular prostheses in cases of enucleation secondary to ocular malignancy and severe traumatic eye injuries; furthermore, it may assist in the complex process of orbital reconstruction following these conditions. Sébastien et al. presented the first customized patient–tailored ocular prosthesis designed with the aid of 3D printing for a patient with acquired anophthalmos secondary to evisceration. The ocular prosthesis was based on a 3D-printed mold of the anophthalmic socket of a 68-year-old male who was successfully fitted. According to Sébastien, production of 3D-printed ocular prostheses began in 2013; however, these prostheses were initially mass-produced in three pre-defined sizes and in preselected hues, thus not tailored to the individual patient [41]. Tarjani Vivek et al. described how 3D printing can be utilized for the customization of patient-specific implants for the management of inferotemporal spherical orbital implant migration (decentration and displacement) in six patients (ages 3–47) with prior socket surgery [42]. By applying 3D-printed implants in the basin of the inferior orbital fissure, pushing the migrated implant into the intraconal space, they managed to achieve re-centration of the migrated spherical implant, both clinically and radiologically. Postoperative complications were not seen over a mean follow-up period of 21 months with patient satisfaction with the outcome of the procedure. The cost of the 3D-printed model was estimated at $5 USD, compared to contemporary implants which cost $350 USD. A retrospective analysis of 29 cases that underwent 3D technique–assisted orbital fracture reconstructive surgery, as compared to 27 cases that underwent traditional surgery, showed a shorter surgery duration and statistically significant lower maximum width, depth, and area between fracture zone and the implant in the 3D group. The 3D group received biocompatible material composed of titanium mesh and porous polyethylene (Medpor-Titan mesh) shaped and trimmed according to their personalized 3D anatomical model of the orbit contour. In addition, the difference in the medial-inferior wall angle between the surgical eye and healthy eye was also statistically significantly different between the two groups. A postoperative clinical evaluation was found to be superior in the 3D group, as compared to the control group [43]. A retrospective case series of five orbital reconstructions utilizing 3D printing of orbital implant templates was presented by Callahan et al. This study described three cases of tumor reconstruction and two cases of orbital fracture reconstruction using Medpor-Titan implants in four of the cases and titanium mesh in one. Four of these cases were complex secondary reconstructions. Callahan et al. demonstrated that low-cost patient-tailored implant printing is achievable for orbital reconstruction and can be applied to the surgeon's preferred implantable material [44]. In 2015, Furdová et al. described a new modality for the visualization of intraocular tumors prior to linear accelerator–based stereotactic radiosurgery. Five polylactic acid–based colored models of eyes with uveal melanoma were created from CT and MRI data with an estimated printing time of 15 to 30 min per model. The models included the sclera, cornea, lens, optic nerve, and the tumor mass [45]. These models assisted the physician to better localize the tumor borders as compared to standard 2D radiographic imaging. Utilizing 3D models with the goal of improving clinical outcomes may be achieved by increasing the surgical experience and dexterity for a particular case prior to entering the operating room with the actual patient. In 2017, Bannon et al. described a 3D printing method that can be utilized for medical staff education. In their study, they discuss an approach to create a low-cost 3D model of the pterygopalatine fossa, which is considered a complex anatomical region to understand due to its poor visualization during cadaveric dissections. They were able to provide a useful and innovative aid for understanding the complex anatomical relationships of this region [46]. 3D-printed high-resolution reproductions of cadaveric orbital dissections from different views, suitable for education and training, were printed by Australian physicians and scientists in a method suitable for rapid reproduction. This approach carries the benefit of avoiding cultural and ethical issues associated with dissecting and studying actual cadaver specimens [47]. A similar process for creating low-cost personalized orbital models for use in orbital surgery training using 3D printing technology was described by Scawn et al. [48]. 3D printing can assist in designing and producing low-cost and accessible ocular accessories, such as spectacles and contact lenses. Ayyildiz et al. described a novel method for prototyping and manufacturing customized 3D–printed spectacles that can be applied to patients with facial deformities and unusual facial features [49]. The time required for 3D printing the spectacles was 14 h and the cost to manufacture was estimated at $160 AUD. Optical alignment, good comfort, and acceptable cosmetics were achieved; even a month after fitting, the 3D-printed spectacles did not require further attention. Rigid gas permeable contact lens (RGPCL) fitting, especially for patients with an irregular corneal surface, can be both customized and produced more efficiently with 3D printing. Preliminary experimental results, as shown by Zhao et al. indicate that this method effectively reduces the number of try-ons needed to determine correct contact lens parameters and increases patient satisfaction, while decreasing the long-term risk of epithelial abrasions and infection [50]. In 2017, Johnsons & Johnsons launched several collaborations with a goal of developing 3D-printed personalized contact lenses [51]. In a different field, a 2018 report demonstrated how 3D printing can be used to rapidly design and manufacture custom-made low-cost eyelid crutches as an alternative solution to the surgical treatment of blepharoptosis caused by progressive myopathy [52]. Custom-made surgical instruments are yet another field of 3D manufacturing. Printing a customizable trocar-cannula system for vitreoretinal surgery was successfully achieved as part of a feasibility study published by Navajas and Ten Hove in 2017. The system was tested on pig eyes and although one canula broke during insertion, it was clearly demonstrated that 3D printing has the potential to produce a functional trocar-cannula system with a customizable optimal blade profile, length of cannula shaft, and ergonomic handle [53].

Ocular devices such as fundus cameras and slit lamps are expensive, with a price tag out of reach by most general practitioners and primary healthcare providers. In 2015, Hong described a 3D-printed slit lamp microscope adapter for smartphones at a production cost of a fraction of the price of conventional equipment. This device can image and document anterior segment pathologies. Moreover, he described a portable 3D–printed retinal imaging adapter for mobile phones. According to Hong, the entire printing process takes less than 3 h with an estimated cost of $5 USD per unit. Such devices can transfer data electronically to ophthalmologists around the world and are readily available for rural and underdeveloped regions, enabling local medical staff to rapidly and accurately diagnose and treat common ocular disease [54, 55]. Sixteen-year-old Kavya Kopparapu developed a 3D-printed lens that can be attached to a smartphone and used to diagnose diabetic retinopathy. Diagnosis rates were reported to be comparable to those of an ophthalmologist. Diagnosis was achieved by analyzing the smartphone-generated photographs by an automated machine–learning algorithm, known as a convolutional neural network. Such devices can potentially improve screening efficiency and increase availability to populations at need. This concept was put to the test at the Aditya Jyot Eye Hospital in Mumbai, India [56, 57].

Conclusions

3D printing first appeared three decades ago. Nevertheless, the implementation and utilization of this technology in healthcare became prominent only in the last 5 years, with an exponential rise in 3D-printed healthcare-related objects and devices. The potential applications of this technology in ophthalmology are extensive, and the purpose of this review is to raise awareness among ophthalmologists and report current and future uses. 3D printing has the advantage of low-cost production of customized devices and prostheses, easy development and design, fast production, and the ability to produce a single item at a time, each unique in shape and design. Such products may be as diverse as instruments that aid in early detection of common ocular conditions, devices, whether diagnostic of therapeutic, built specifically for individual patients, 3D-printed contact lenses and intraocular implants, models that assist in surgery planning, improve patient and medical staff education, and more. Advances in bioprinting appear to be the future of 3D printing in healthcare in general, and in ophthalmology in particular, with the emerging possibility of printing viable tissues and ultimately the creation of a functioning cornea, and later retina. One day, perhaps, research groups might start work on the greatest challenge of all, “printing” an entire eye that might become one day in the distant future, a viable option for restoring vision.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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