Personalized Medicine Goes 3D

3D printing is no longer on the horizon. The future is now, and clinical applications will be arriving soon across all subspecialties.

By Mike Mott, Contributing Writer

LAST NOVEMBER, OPHTHALMOLogists at Moorfields Eye Hospital in London achieved a first: a patient was fitted with a 3D-printed prosthetic eye. Following a noninvasive, multisecond scan of the socket and existing eye, the ophthalmic team created a 3D model from the data, which was then used to print the prosthetic in color, layer by layer.

This is just the beginning of innovations that could disrupt the delivery of ophthalmic care, said Cristos Ifantides, MD, at the University of Colorado in Denver. From prostheses to implants, drug delivery, surgical simulators, and tissue regeneration, additive manufacturing is proving that "bespoke" isn't just a buzzword, he said.

"Many aspects of our practice are much more personalized than [that which occurs] in other fields in medicine, but they don't quite reach a truly custom-made designation," he said. "Our capsular tension rings, our glaucoma drainage devices, and our IOLs are all designed for groups, not individuals. But 3D printing has the potential for a truly individualized medicine based on the specific measurements of a specific patient."

A Unique Morphology

3D printing is a layered manufacturing technology that got its start in the 1980s, with patents and designs that would later fuel commercial uses in industries ranging from automotive engineering to architecture. The "maker" movement then brought 3D printing into the mainstream in the late 2000s. Today, with the expiration of many of the earlier patents, commercial printer manufacturers number in the hundreds.

Medical applications of this technology have already proven to be advantageous, most notably in dentistry and orthopedics. Ophthalmology, however, has fallen behind some of its peers, and that's due in part to the anatomy of the eye itself, said Andrea A. Tooley, MD, at the Mayo Clinic in Rochester, Minnesota. "From the cornea to the posterior segment to the ocular socket, the eye is a highly complex and specialized organ that's also made up of incredibly small parts," she said. "And it's this complexity that has introduced challenges because some printing applications will need to operate at the thickness of a micron."

This complexity also has its benefits, said Dr. Ifantides. The eye's unique immune privilege creates an ideal environment for different therapies. Moreover, its many different moving parts allows for very specific 3D printing applications. "3D printing as applied personal medicine is specifically well suited for ophthalmology," he said.

Use in Planning and Education

As early as 1994, clinicians demonstrated the benefits of patient-specific 3D models for planning craniofacial surgery.[1] This technology is now helping ophthalmologists better visualize patient anatomy, simulate complex procedures, and prepare the next generation of surgeons.

Simulation. With the help of 3D printing, ophthalmologists can improve their clinical outcomes by being able to simulate a procedure on

Cynthia Turner

a model that's specific to the patient, said Mandeep S. Sagoo, MB, BChir, PhD, FRCS, FRCOphth, at Moorfields. "If you have a complex piece of anatomy on which you need to perform a very difficult operation, this technology can allow you to take a CT scan and 3D-print a model of the tissue or organ in question," he said. "You then have a sandbox in which to operate, because when it's time for the actual procedure, you've preplanned your exact steps, which can help improve your confidence and make the experience quicker and easier for you and your patient."

Visualization. Researchers have demonstrated the feasibility of this approach for helping visualize everything from orbital repair to keratoplasty to strabismus surgery. A 2019 study, for example, simulated complex Descemet membrane endothelial keratoplasty using human corneas that were mounted on an artificial anterior chamber with a 3D-printed iris.[2] This allowed the researchers to adjust the anterior chamber depth and pupil size and, as a result, vary the surgical difficulty and better emulate the nuances of the live procedure.

Training. 3D printing technology also has enormous consequences from an educational standpoint, said Dr. Tooley, as it can speed up a trainee's ability to grasp concepts faster without the need for actual tissue. "Learning surgery is always challenging because of access to animal and cadaver eyes," she said. But with 3D-printed models, residents can quickly learn how to insert a 3D-printed glaucoma valve or how to realign bones on the orbit. They could also learn how to correct pathology by using 3D models with high-fidelity tissue that mimics advanced disease states.

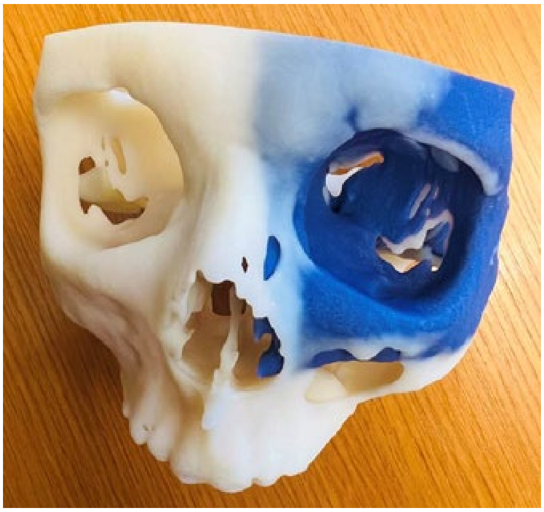
A recent study by a Canadian team offered a 3D-printed solution for one challenge: creating eye mounts that are customizable, cost-effective, and replicative of actual patients' facial anatomy.[3] Employing a commercially available 3D printer, the research team's novel eye mount featured a biodegradable polylactic material that emulates natural facial contours as well as an open-source design that allows for widespread use.

Oculoplastics Leads the Way

At the moment, the most applicable use of 3D printing in ophthalmic practice is in oculoplastics, said Dr. Tooley.

Given the larger size of the custom molds, there isn't the same demand on printing resolution and tolerance compared to smaller medical applications. "That—combined with the widespread availability of imaging technologies—has made oculoplastics a great field for championing the benefits of 3D printing," she said.

Surgical guides and implants. Dr. Tooley and her colleagues regularly use both 3D-printed surgical guides and implants for reconstruction in cases of trauma and craniofacial deformities. "These guides are a great resource for surgeons in the OR because they are an exact print of your patient's facial structure," she said. "This type of real-time familiarization with patient-specific anatomy can dramatically cut down on your operating time and increase your surgical accuracy."



3D-PRINTED ORBITAL MODEL. *The "normal" anatomy of the patient's right side (white) has been mirrored onto an orbital floor defect on the left (blue) in order to help contour an orbital floor implant for surgical planning.*

Andrea A. Tooley, MD

Custom 3D-printed implants have also proven to be particularly useful in applications involving unilateral orbital surgery and craniofacial reconstruction, said Dr. Tooley. "Our most common application involves scanning the unaffected side of the facial structure to produce a mirrored implant for the affected area," she said. "This is particularly helpful because it takes out the guesswork that often occurs when you're trying to match one side to the other and the anatomic landmarks of the structures aren't consistent due to trauma."

Learning curve. Surgery using 3D-printed models does come with challenges, Dr. Tooley noted. For example, during a recent operation, Dr. Tooley and her neurosurgical colleagues employed a custom implant that incorporated a unique characteristic that they saw on a preoperative scan. However, the implant wasn't a good fit. "After surgery, the implant was too large, and we had a difficult time trimming it down because of its size and because these custom-based products aren't intended to be tailored on the fly," she said.

Despite the learning curve, several recent studies are showing the impact that 3D printing can have in clinical practice. One review found that the repair of orbital floor fractures using a 3D-printed mold cut surgery time by almost half.[4] A similar study found that 3D printing not only resulted in shorter surgical duration compared to conventional methods but also produced significantly better implant fit and postoperative outcomes.[5]

Printed Prosthetics

Computer-aided scanning and mapping of the orbital socket allowed for the earliest use of 3D printing in eye care. The same technology is now changing the landscape of ocular prosthetics.

Ocularists—who fabricate and fit ocular prosthetics—are true artists, said Dr. Tooley. And while that artistry is essential, it comes with a cost. "They are incredible at what they do," she said. "Painting custom prostheses by hand is meticulous and painstaking work, and their products are beautiful—but they are also very expensive, and patients are often left on lengthy waiting lists."

3D printing won't make ocularistry obsolete, said Dr. Sagoo, but it will disrupt the entire manufacturing process. He leads the same Moorfields team that fit the first fully 3D-printed prosthetic eye last November and knows firsthand the potential for this technology to produce the implants quickly and cheaply.

The printing process. Dr. Sagoo's multidisciplinary team of ophthalmologists, engineers, ocularists, and photography specialists still are experimenting with the manufacturing process, but their current system allows for prosthetic eyes that offer clearer definition and depth compared with those produced via conventional manufacturing.

"We started by developing a specialized OCT that's able to scan the socket, providing us with essentially an impression mold after the eye is removed," said Dr. Sagoo. That's also where they reached their first hurdle: the OCT was unable to scan underneath the eyelids and thus couldn't provide a complete map.

With machine learning algorithms in tow, however, the team was able to quantify the correct socket shaping for the posterior portion of the prosthetic. "The existing eye then served as our template for the front-facing architecture of the prosthetic eye," said Dr. Sagoo. "With an additional color-calibrated sensor attached to the OCT, we took a color photo of the eye that provided us with the contours and shape of the cornea, iris, and anterior chamber."

The compiled data were fed into a specially calibrated 3D printer that can then print in hours something that would take an ocularist days to make by hand. The result: the first ocular

3D Printing as a Disruptive Technology

It's difficult to find a single aspect of ophthalmic practice that won't be significantly impacted by 3D printing, said Dr. Ifantides. For example, bespoke surgical instruments can be custom printed to match the exact specifications of an individual surgeon, thus cutting the costs of prototypes for instrument manufacturing.

Focus on IOLs. One market that could be the most disrupted is IOL manufacturing, said Dr. Ifantides. IOLs are a billion-dollar industry that dominate the ophthalmic device market around the world. And without a doubt, manufacturers will be investing heavily in 3D printing technology when the time comes, he said.

In the meantime, researchers are currently testing the feasibility of patient-specific IOLs. Many studies have reported acceptable transparency and optical indexes in 3D-printed prototypes.[1,2] However, significant surface irregularities have been noted, and optimal biomaterials for IOLs remain under investigation.

"We're in the early stages here, but 3D-printed lenses will hopefully provide us with another layer of creativity to better deliver personalized care," said Dr. Ifantides. 3D printing could allow for multiple optic sizes and the ability to change the shape of the IOL to reduce dysphotopsia, he said. And in the future, the infusion of antibiotics, steroids, and other drugs into 3D-printed lenses could help eliminate drop burden and improve overall patient compliance.

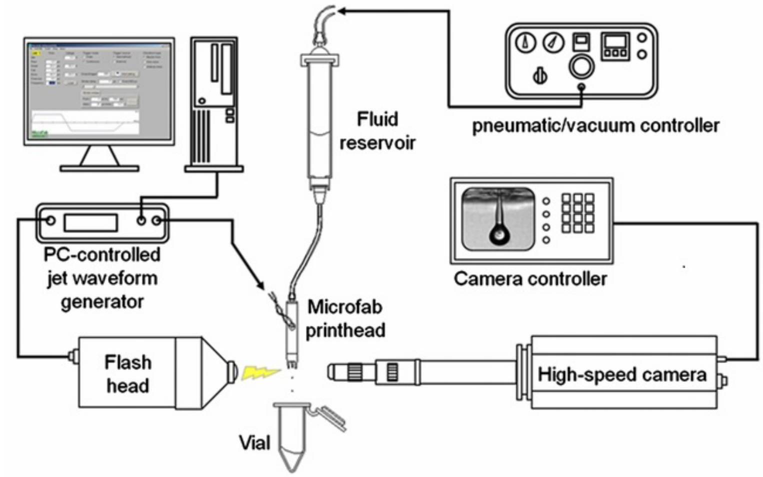
Other applications. Beyond IOLs, 3D-printed glaucoma valves are just one type of ophthalmic device that could change supply chain dynamics altogether and help fill the medical needs of ophthalmologists in settings with limited resources. Personalized eyewear can even be designed with customized eyecups that create an anatomically correct moisture chamber to benefit patients with dry eye.

And drug delivery also is in play: neurologists treating epilepsy, for example, were the first physicians to reap the benefits of a 3D-printed pharmaceutical in 2015 when the FDA approved a pill designed to dissolve in seconds when in contact with liquid.

1 Debellemanière G et al. *J Refract Surg.* 2016;32(3): 201-204.
2 Li JW et al. *Int J Ophthalmol.* 2020:13(10):1521-1530.

prosthetic that was fully 3D-printed, layer by layer, in color.

Clinical trial. Dr. Sagoo and his team are now putting this process to the test in a phase 1/2 randomized clinical trial.[6] For this study, 40 patients will wear the 3D-printed prosthesis or the handmade analog for a four-month period and then cross over to wearing the alternative prosthesis for an additional four months. The researchers hope to assess movement, cosmesis, comfort, and any adverse effects, such as mucous discharge.



PIEZOELECTRIC PRINTING. *Schematic of the inkjet printing and imaging apparatus used to print purified retinal glial and dissociated retinal cells.*

"Our hope is that we can fine-tune the anatomical correctness of our digital prosthetic to better mimic all the markings, crimps, and depths of an actual eye," said Dr. Sagoo. Trial enrollees will include those who have a stable socket without any surrounding inflammation, he said. That's because the 3D-printed prosthetic is currently best suited for patients without complex orbits.

More complicated cases might still require conventional handmade manufacturing, but Dr. Sagoo believes up to 70% of patients needing an ocular prosthetic will be able to take advantage of 3D-printed alternatives in the future.

On the Horizon: Bioprinting

It might sound like science fiction, but bioprinting human tissue is an emerging technology that could greatly impact biomedical applications such as regenerative medicine and pharmaceutical testing, said Keith R. Martin, MD, FRCOphth, at the University of Melbourne in Australia.

Similar to other forms of 3D printing, bioprinting involves the layer-by-layer deposition of biological inks in highly precise spatial arrangements to create cell-based structures. These "bioinks" are typically a suspension of living cells combined with a biopolymer gel that serves as a scaffold around which the cells can proliferate.

Initial applications. Bioprinting was first demonstrated in 1988.[7] Since then, the technology has made significant advances across cardiology, dermatology, and neurology. An important medical first occurred in 2013 when physicians at the University of Michigan successfully implanted a 3D-printed bioresorbable tracheal splint in a child with bronchial malacia.[8]

Making its way into ophthalmology. Bioprinting also is making headway in ophthalmology, but it may be a long time before it lives up to its game-changing potential, said Dr. Martin. "Simply put, making organs is difficult," he said, "but compared to a structure like the brain, the eye is showing to be a great environment for this type of experimentation given its relatively well-organized layered structure and its distinct cell types."

Cornea. Because it's one of the most frequently transplanted tissues, the cornea is a natural target for 3D printing, Dr. Martin said. Its relatively homogenous cell structure lends itself well to bioprinting technology, although it remains to be seen whether 3D printing will have sufficient advantages over other methods of corneal bioengineering to drive uptake of this technology in the future, he noted.

Pioneering researchers in the United Kingdom successfully printed a corneal stroma in 2018.[9] Using a collagen-based bioink that contained human corneal keratocytes, they were able to engineer a highly viable cornea within minutes. (The team also noted the technology's ability to create custom corneas based on scans from an individual patient.) More recent studies have replicated this success with stromal tissue regeneration, demonstrating that the biomechanical properties of 3D-printed corneal cells can approach those of the native cornea and with excellent transparency.[10]

Despite these advances, it will be several years before a fully complete, multilayer cornea will be available for transplantation, said Dr. Sagoo. Further testing will be needed to show that bioprinting can ensure long-term mechanical strength, cell survival, and transparency in humans.

Retina. The retina—although it's a more complex structure—might hold considerable promise for bioprinting applications, Dr. Martin said. In 2013, he and his team made headlines when they used piezoelectric inkjet technology to print a rat retina's ganglion and glial cells.[11] To their surprise, the cells not only survived the process but also continued to grow in culture.

In piezoelectric printing, an element ejects liquid drops from a nozzle in a fashion similar to that used in commercial inkjet printers, said Dr. Martin. His team used four of these print heads to sequentially print multiple cell-laden inks that would make up the cellularized retinal tissue. "The most difficult part was getting the viscosity of the medium and nozzle diameter right, because this was a case of educated guessing at first," Dr. Martin said. After a bit of trial and error, the team wound up with a frequency of 1,000 hertz—the equivalent of 1,000 tiny droplets, each containing an individual retinal cell, fired out every second.

"The fact that the cells survived following the spray was a bit shocking," said Dr. Martin. "Often, retinal ganglion cells seem to die with even the slightest provocation. But they survived and continued to grow after a flight distance of about 10 millimeters into a vial."

Dreaming Big

With additional development, bioprinting could open up an opportunity for engineering grafts to address macular holes and other retinal defects, said Dr. Martin. The piezoelectric technology also holds the potential to change the fundamentals of retina surgery. "Down the road, there's no reason why we couldn't perform the actual bioprinting inside the eye itself," he said. "The technology will be there, and it will be testable. Imagine having a print head at the tip of a vitreoretinal instrument that allows you to spray new, viable retinal pigment epithelial cells directly on the damaged area. It's not outside the realm of possibilities."

In the end, dreaming big will be the driving force for how 3D printing can better serve you and your patients, said Dr. Ifantides. "Henry Ford said it best: 'If I would have asked people what they wanted, they would have said faster horses.' So it's time to think beyond the tools we *have* at our disposal and imagine the tools we *want* at our disposal."

PRINTED PROSTHETIC. *A 3D-printed prosthetic eye, showing layer-by-layer manufacture.*

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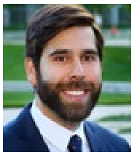

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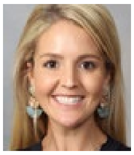

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