Aesthetic reconstruction of microtia: A review of current techniques and new 3D printing approaches

Maureen T Ross[a*], Rena Cruz[a], Courtney Hutchinson[a], Wendy L Arnott[b,c], Maria A Woodruff[a], Sean K Powell[a]

[a]*Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia;* [b]*Research and Development, Hear and Say Centre, Ashgrove, Queensland, Australia;* [c]*School of Health and Rehabilitation Sciences, The University of Queensland, Brisbane, Queensland, Australia*

*MT Ross; P: +61 432996350; E: maureen.ross@connect.qut.edu.au; A: QUT, P Block, Gardens Point Rd, Brisbane, QLD, Australia 4000

R Cruz; E: rena.cruz@hdr.qut.edu.au; A: QUT, P Block, Gardens Point Rd, Brisbane, QLD, Australia 4000

C Hutchinson; E: courtney.hutchinson@qut.edu.au; A: QUT, P Block, Gardens Point Rd, Brisbane, QLD, Australia 4000

WL Arnott; P: +61 738502111; E: wendy.arnott@hearandsay.com.au; A: 29 Nathan Avenue, Ashgrove, QLD, Australia 4060

MA Woodruff; P: +61 7 31387778; E: mia.woodruff@qut.edu.au; A: QUT, P Block, Gardens Point Rd, Brisbane, QLD, Australia 4000

SK Powell; P: +61 432481008; E: sean.powell@qut.edu.au; A: QUT, P Block, Gardens Point Rd, Brisbane, QLD, Australia 4000

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Three dimensional (3D) printing and biofabrication technologies are revolutionising medicine with low-cost and novel treatments for complex medical conditions. These approaches differ from traditional treatments by using 3D scanning, computer modelling and 3D printing to automate the production of patient-specific tissue replacement or prostheses using a wide range of materials. One area impacted by this technology is the treatment of congenital maxillofacial conditions such as microtia, a condition affecting the intrauterine development of the auricle (external ear) and with a prevalence of 2.06 cases for every 10,000 births. While not life-threatening, microtia significantly impacts the emotional and psychological wellbeing of the affected child and their parents and is often accompanied by malformation of the external auditory canal and associated conductive hearing problems. Current treatments include the use of prosthetic ears or surgical methods such as autografting rib cartilage or alloplastic implants. Although current options have shown documented success, they are highly dependent on the surgeon's skill and it has been demonstrated that poor quality solutions can further exacerbate negative psychosocial impacts. As such, higher quality, lower cost and more customised options would be welcomed by patients and parents alike. Recent advances in 3D scanning, modelling and printing techniques have clear applications in prosthesis manufacture which could significantly benefit the treatment and reconstructive options for children with microtia, leading to improved quality of life.

Keywords: microtia, reconstruction, 3D scanning, 3D printing, 3D modelling, tissue engineering, prosthesis

Introduction

Congenital defects and trauma often require intervention in the form of reconstructive surgery or the use of prostheses to aid treatment and recovery. One such congenital condition, microtia, is characterised by structural abnormality of the auricle (outer-ear) (Kelley and Scholes 2007, Cabin et al. 2014). The condition occurs in approximately one in every 5,000 births worldwide (Luquetti et al. 2011). Microtia can affect the orientation, size, relief pattern, position of the outer-ear. In some cases, there is total absence of the outer ear which is termed artresia. Microtia is also associated with conductive hearing problems, with 76% of microtia patients having atresia of the ear canal preventing sound from reaching the inner ear (van Nunen et al. 2014, Ishimoto et al. 2007). Other hearing issues can include sound localisation difficulties due to the lack of an external ear which can direct sounds into the ear canal (Kaga, K., & Asato, H. 2016). This also results in a reduced ability to recognise speech in noisy environments, affecting a child's learning potential in school (Walsh et al. 2008). More profoundly are the significant emotional and psychological impacts for children and their families (Li et al. 2010, Jiamei et al. 2008, Horlock et al. 2005, Johns et al. 2015). Children with microtia often show signs of anxiety, depression and have marked difficulty with social interaction (Horlock et al. 2005, Johns et al. 2015, Li et al. 2010). Restorative treatments such as auricular reconstruction have demonstrated improved psychosocial outcomes amongst patients, including less self-reported and parent-reported teasing from peers (Jiamei et al. 2008, Horlock et al. 2005, Johns et al. 2015, Johns et al. 2016, Steffen et al. 2008, Storck et al. 2014). Given these improvements, low-cost access to treatments that restore the natural aesthetic of each patient's ear is important.

Traditional treatments involve either hand-made prostheses or surgical approaches such as alloplastic implants or autogeneous cartilage reconstruction. These approaches have been life-changing for many patients, but require specialised surgeons, and lead to an increase

in cost. Advanced manufacturing technologies promise to revolutionise many industries offering a highly personalised, rapid, and automated solution. Underpinning this are innovations in digital 3D scanning, 3D computer modelling, and 3D printing and biofabrication processes. Given its advantages over traditional manufacturing techniques, is not surprising that this technology has important applications in medicine. A 3D scanner can be used to non-invasively capture accurate morphological detail of the patient's anatomy, which is then computer-processed to produce a digital customised 3D model. This model is then sent to a 3D printer and the desired 3D physical object formed in a layer-by-layer manner. The 3D printed patient-specific solution can then be either temporarily attached to the patient in the case of prostheses, or surgically implanted in the case of permanent sterile, biocompatible scaffolds.

The present review outlines the current clinical approaches to treating microtia and the hurdles associated with these. The focus of the review will then shift to the current research efforts in 3D scanning, advanced manufacturing and biofabrication approaches for creating patient-specific treatments for aesthetic restoration of the external ear.

Microtia

Congenital microtia describes the broad spectrum of auricle deformities that occur during the embryonic stages of development. The worldwide prevalence of microtia is 2.06 cases for every 10,000 (Luquetti et al. 2011). It is more likely to be unilateral (affecting only one side in ~87% of cases) with the right ear more commonly affected (~62% of unilateral cases) (Castilla and Orioli 1986, Brent 1999, Forrester and Merz 2005, Paput et al. 2011, Canfield et al. 2009, Suutarla et al. 2007, Van Nunen et al. 2014). Microtia often associated with aural atresia, the failed development (i.e. hypoplasia or narrowing) of the external auditory canal (Kelley and Scholes 2007, Suutarla et al. 2007, Van Nunen et al. 2014).

Marx (1926) developed a classification of four grades (or degrees) of microtia (Figure 1). First degree describes the case where the auricle is slightly small for size. Second degree describes the case of greater deformity, where the helix or lobule of the ear are absent. Third degree microtia is often defined as a "peanut" shaped deformity where only a remnant of the auricle is present. Complete absence of the auricle, also referred to as anotia, is considered fourth degree (Marx 1926).

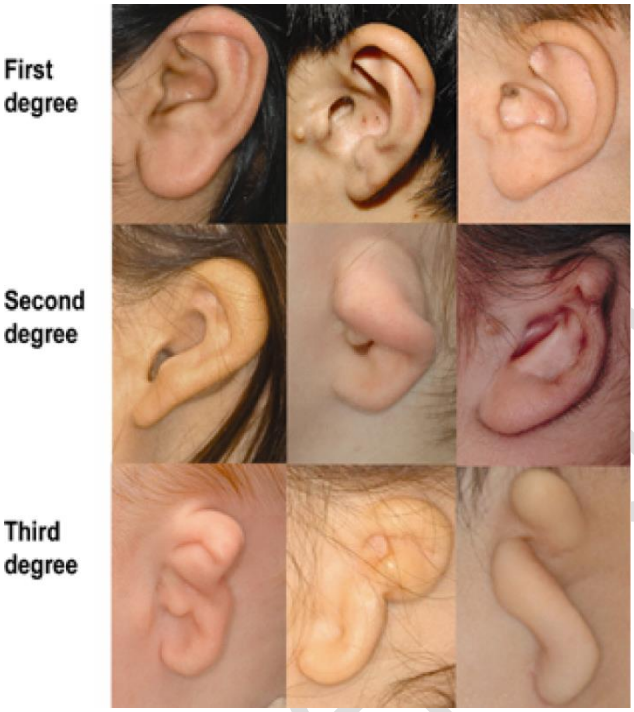

Figure 1. Examples of first degree microtia (slight malformation and most structures recognisable), second degree microtia (moderate malformation and some normal auricle structures recognisable) and third degree microtia (severe malformation and no normal pinna structures are detectable). *Reproduced with permission from* (2013) *Wiley* (Luquetti et al. 2013).

Traditional treatment techniques

Treatments for microtia can be broadly separated into external prostheses and surgical reconstruction, with the aim to restore the aesthetic of the natural ear (Figure 2). Typically, prosthetic ears are a non-permanent treatment option made from medical grade silicone to

mimic the look of the natural skin. Permanent surgical reconstruction options include an autologous approach, harvesting the patient's own costal (rib) cartilage, or an alloplasty with a commercially available high-density, porous-polyethylene implant.

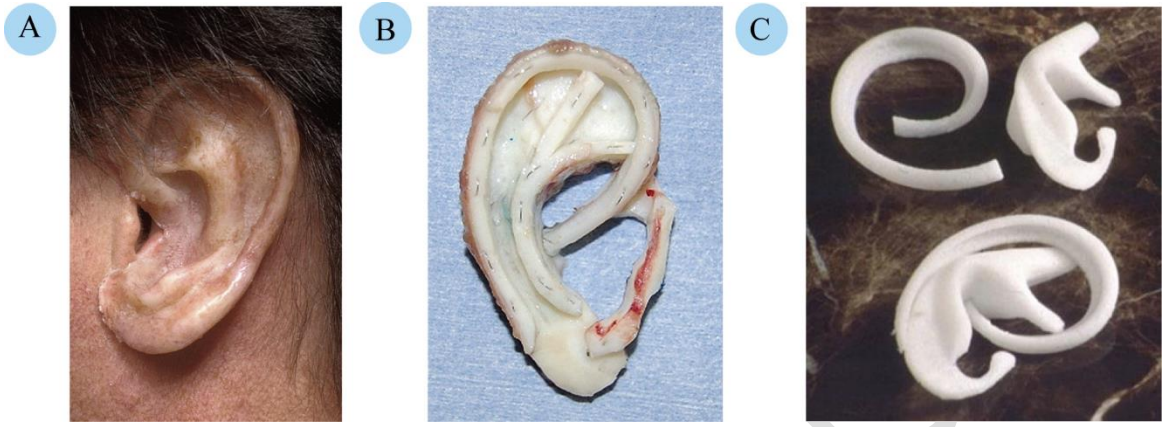

Figure 2. Microtia reconstruction solutions A) silicone prosthesis, B) autograft from costal cartilage, C) Medpor polyethylene implantation. *Reproduced with permissions from (2010) (2011) Elsevier (Younis et al. 2010, Sabbagh 2011)and (2008) Thieme.(Romo and Reitzen 2008)*

Hand-made Prosthesis

Auricular prostheses are classically manufactured using room-temperature vulcanizing (RTV) medical grade silicone through a lengthy manual process that requires up to 14 hours of labour (Butler et al. 2000, Louis et al. 2013, Storck et al. 2014). Due to the high labour these prostheses have been recorded to cost between $2,000 and $7,000 (Saadi and Lighthall 2017). The prosthesis can be attached to the patient by adhesive, or titanium osseointegrated implants (Storck et al. 2014, Hamming et al. 2009, Nichols et al. 2014, Arora et al. 2016, Younis et al. 2010). Osseointegrated implants can be of two types; magnet or bar and clip (Hamming et al. 2009, Louis et al. 2013, Nichols et al. 2014, Arora et al. 2016, Younis et al. 2010). Adhesive attached prostheses are a good option for those who are unable to undergo large multi-step surgery (Storck et al. 2014). The advantages of choosing osseointegrated implants over adhesives include a stronger hold, easier placement, improved lifespan of the prosthesis and reduced skin irritation (Louis et al. 2013, Arora et al. 2016, Storck et al. 2014). The

disadvantages however, include the care and maintenance requirements, risk of infection, inflammation, granulation of skin or haematoma and the increased surgeries (Louis et al. 2013, Storck et al. 2014, Hamming et al. 2009, Nichols et al. 2014, Younis et al. 2010).

Silicone has many properties well suited to prosthesis hand-manufacturing such as it being easy to form, intrinsically colour and extrinsically stain and seal (Louis et al. 2013, Arora et al. 2016, Storck et al. 2014, Butler et al. 2000). However the material is disadvantaged by its low tear strength and discolouration from exposure to elements such as sunlight, resulting in a typical life of two to five years before a replacement is required (Louis et al. 2013, Arora et al. 2016, Hamming et al. 2009). Butler et al. (2000) describe a common method of prosthesis fabrication which begins with taking a plaster cast of both the microtia affected ear and the unaffected ear. In the case of bilateral microtia, another person's ear can be used as the design model. Using these plaster casts, a wax prototype is sculpted and refined before being placed on the patient to adjust and match the proper angulation of the ear (Figure 3). Handheld tools are then used to recreate the surface and texture of the ear onto the wax model. The sculptor then creates a three piece dental mould using the wax prototype. This mould is initially lined with a thin layer of silicone to recreate the superficial vasculature, pigmentation and surface irregularities of the ear. It is then filled with a more silicone and once cured further aesthetic changes are painted on. Given the high cost of labour to produce a prosthetic ear with these methods, the need for a cheaper alternative, with the possibility of a greater lifespan would be welcomed by patients (Butler et al. 2000).

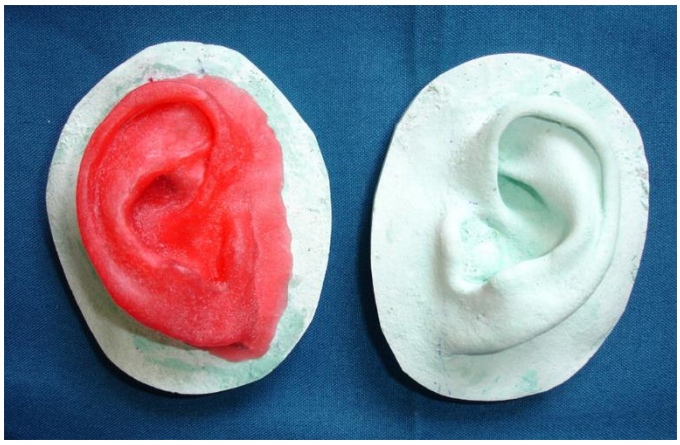

Figure 3. A wax prototype of the ear prosthesis that was sculpted based on the plaster cast of the unaffected ear. *Reproduced with permission from (2007) Elsevier (Subburaj et al. 2007).*

Surgical reconstruction

There are two permanent surgical techniques available for auricular reconstruction; autografting and alloplasty. Autografting involves harvesting costal cartilage from the patient, which is subsequently shaped by the surgeon into the inner cartilage framework of the ear (Romo and Reitzen 2008, Otto et al. 2015, Park et al. 2016). Alloplastic implants are made of high-density porous polyethylene; a stable and inert, non-reabsorbable thermoplastic which is manufactured into a standard ear cartilage shape (Romo and Reitzen 2008, Otto et al. 2015, Zhao et al. 2016, Cabin et al. 2014, Storck et al. 2014, Tollefson 2006). These are most commonly manufactured under the name Medpor® (Stryker, Minnesota, US). 91.3% of surgeons choose autografting over alloplasty as their preferred reconstruction choice (Im et al. 2013). As such, autografting is considered standard treatment for microtia (Xu et al. 2005, Reiffel et al. 2013, Zhao et al. 2016, Baluch et al. 2014, Im et al. 2013).

Tanzer (1959), developed the technique of carving autogenous costal cartilage in the 1950s which was a major revolution in the field of auricular reconstruction. This method of reconstruction is still regarded as the gold standard for microtia; however, it is also considered one of the most difficult operations in plastic surgery (Sabbagh 2011, Kludt and Vu 2014,

Zhao et al. 2016). Brent (1999) and Nagata (1994a), (Nagata 1994b, Nagata 1994c) pioneered current methods for autografting. Brent's technique is a three or four stage process, which harvests less cartilage than the Nagata technique, therefore allowing for younger children to undergo the surgery (eight to nine years old) (Storck et al. 2014, Kelley and Scholes 2007, Brent 1999, Sabbagh 2011). The Nagata technique requires fewer stages, however the technique is more challenging as it requires additional carving of the cartilage which forms the ear, plus it requires patients to be 10 years old with a minimum chest circumference at the xyphoid of 60 cm (Baluch et al. 2014, Kelley and Scholes 2007). Due to the invasive nature of surgery, these techniques present risks of infection and donor site complications including pneumothorax, atelectasis, scarring, thoracic scoliosis and chest-wall deformity (Kludt and Vu 2014, Romo and Reitzen 2008, Puppi et al. 2010, Park et al. 2016). It should also be noted that there are biochemical differences between auricular (elastic) cartilage and rib (hyaline) cartilage, with rib cartilage being much more rigid (Otto et al. 2015, Zhao et al. 2016, Xu et al. 2005).

Medpor implants come as a two-component prefabricated product that is very limited in terms of customisability (Romo and Reitzen 2008, Zhao et al. 2016, Storck et al. 2014, Zeng et al. 2008). Alloplasty has been sought out as an alternative to autogenous transplants as it shortens surgical time and eliminates the need for harvesting costal cartilage and as such, patients can be as young as 5 years of age (Romo and Reitzen 2008, Cabin et al. 2014, Kludt and Vu 2014). However, Medpor implants have been reported to be susceptible to complications such as implant exposure and fracture (Kludt and Vu 2014, Storck et al. 2014, Baluch et al. 2014). To reduce complication rates, patients are required to undergo invasive harvesting of temporoparietal fascia (TPF) to cover the implant and produce a minimal foreign body response (Tollefson 2006, Romo and Reitzen 2008, Storck et al. 2014, Kelley and Scholes 2007, Cabin et al. 2014, Baluch et al. 2014). The TPF is a thin, highly vascular

layer of connective tissue beneath the hair follicles and their surrounding subdermal fibroadipose tissue (Collar et al. 2012). Incomplete coverage of the implant with TPF can lead to infection and loss of the implant. Compression ischemia of the harvested TPF and exposure of the implant are also common issues that have been known to occur (Romo and Reitzen 2008, Cenzi et al. 2005).

Summary of Traditional Techniques

A summary of the treatment options and their advantages and disadvantages is presented in Table 1. It should be noted that the youngest age of intervention is a topic of debate due to a number of factors impacting this decision for both the surgeon and the family including maturity of the ear, available rib cartilage and psychosocial issues (Kelley and Scholes 2007). To minimise aforementioned shortfalls and enable improved patient-specific treatment options, biofabrication is being increasingly adapted into this clinical space.

Table 1. Summary of advantages and disadvantages of traditional treatment options for microtia.

	Removable Silicone Prostheses	**Autograft Reconstruction Rib Cartilage**	**Alloplastic Implant Medpor**
Advantages	Quick, easy way to restore aesthetics for young children or those who cannot, or do not want to, undergo surgery. Silicone is an excellent material to mimic the skin.	Permanent solution. Using the patient's own tissue means there is a very low-risk of rejection by the body.	Permanent solution. Using an alloplastic implant reduces the surgery time for the patient. It also means that the child can be younger (5 years old).
Disadvantages	Hand-made process is time consuming and leads to expensive cost to patient.	The child has to be at least 8 years of age and have sufficient cartilage tissue to harvest. The results can vary greatly depending on	Using a foreign object means there is higher risk of rejection and complications.

	Silicone has low tear strength and degrades from UV light so prostheses have to be replaced every few years.	the harvested tissue and the surgeon's skills. Hyaline cartilage is stiffer and weaker than elastic cartilage.	The rigid plastic can be at risk of fracture or extrusion from the skin. As an off the shelf product there is very little customisation.

How can advanced manufacturing overcome the disadvantages of current treatments?	3D printing would reduce the fabrication process and therefor reduce the cost to patients whilst still providing the same quality product.	Advance manufacturing could assist surgical planning. 3D printing could create personalised implants and tissue engineered solutions harnessing the advantages of autografting and alloplastic implants.

Next generation 3D scanning and 3D printing approaches

3D scanning and advanced manufacturing can have an incredible impact on the way in which clinicians approach reconstruction for microtia (Figure 4). The following section will update the latest research and development into 3D printed ear prostheses, 3D assisted surgery and biofabricated implants.

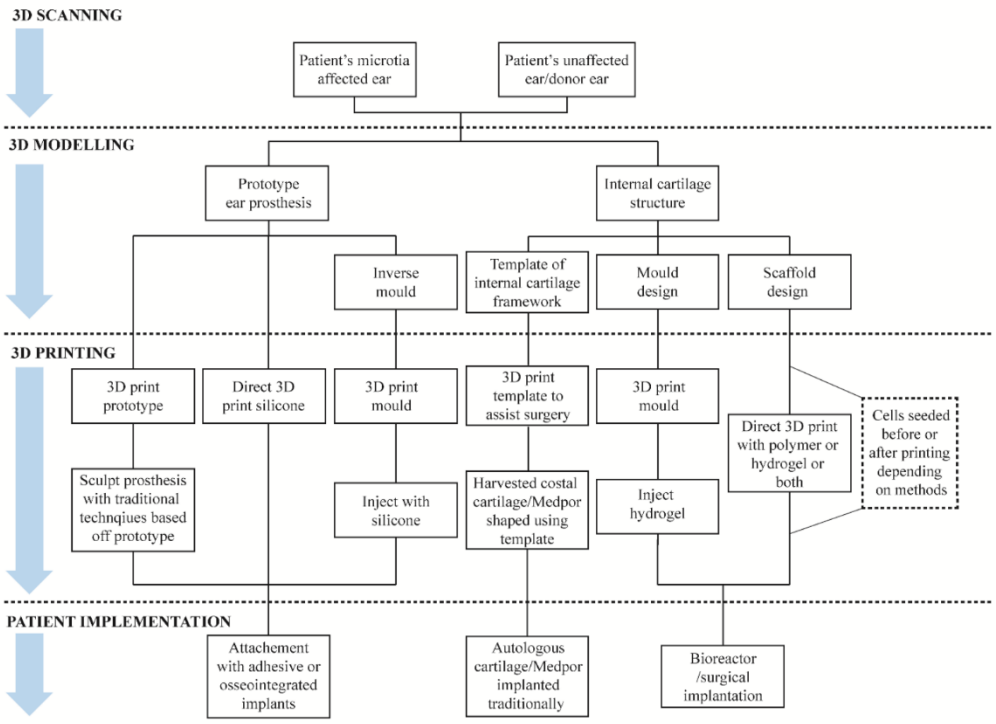

Figure 4. A schematic of the application of 3D patient scanning to 3D modelling and 3D printing of prostheses, surgical planning templates and new tissue engineered implants.

3D scanning and modelling

In the quest to improve treatment options for microtia, accurate 3D patient scanning of both the affected and non-affected ear enables modelling of customised prostheses and reconstructive designs and improves surgical planning. The most common techniques of patient imaging are computed tomography (CT) scanning and magnetic resonance imaging (MRI) (Penkner et al. 1999, Subburaj et al. 2007, Zeng et al. 2008, Liacouras et al. 2011, Kang et al. 2016). Alternatively, surface scanning techniques such as laser scanning (Ciocca et al. 2007, Watson and Hatamleh 2014) and 3D photography (Reiffel et al. 2013, He et al. 2014), have been explored with varying levels of complexity and cost. The most significant advantage of 3D scanning and modelling is the possibility to automate several steps described in the fabrication of handmade prostheses. It also reduces patient discomfort as the technique is much less invasive than moulding using a plaster cast. The main disadvantages are the technical skills required to use the equipment and the related costs of the software and equipment. However, the costs associated with technology decrease every year making it increasing accessible (Ciocca et al. 2007).

CT imaging is most frequently utilized in the literature for capturing 3D data of the patient's microtia affected ear and unaffected ear. This data has been used with computer-aided design/computer-aided modelling (CAD/CAM) technology for a range of approaches. For prosthetics it has been used for prototype design and inverse mould design (Subburaj et al. 2007, Ciocca et al. 2007, He et al. 2014). It has also been shown in increase patient outcomes when used for assisting surgical implantation of osseointegrated implants (Tam et al. 2014). CAD/CAM technology has also been recognised as being beneficial for surgeons in facilitating autologous reconstruction. CT images have been used to create templates of the

cartilage framework to assist surgeons with creating the ear shape from harvested costal cartilage (Berens et al. 2016, Chen et al. 2015). Bos et al. (2015) developed a parametric computer model of the internal cartilage structure of the ear for the same application with the hope it could also be useful for tissue-engineering approaches to reconstruction. The disadvantages of medical imaging is the high cost, exposure to radiation in the case of CT or possible contraindications posed by metal implants in the case of MRI scanning (Liacouras et al. 2011).

Laser scanning is an inexpensive method which builds up a 3D model by using a hand-held scanner that projects a laser against the object. The distance of this laser is used to create a 3D model of the surface of the object which is represented by clouds of points that each have 3D coordinates (Ciocca et al. 2007). Laser scanning eliminates the need for taking impression moulds of the patient's ears and is considerably cheaper than medical imaging. A number of case studies have shown its potential in scan-to-print methodology for creating prostheses for ear and other soft tissue facial applications (He et al. 2014, Ciocca et al. 2007).

Photogrammetry is a similar approach to laser scanning but can be performed using digital cameras making it highly cost effective. The process requires tailor made software which processes photographs and examines their common features. These features are then used as reference points to make a 3D model (Figure 5) (Salazar-Gamarra et al. 2016). Both high end cameras, such as DSLR, and highly accessible smartphone cameras, can be used with varying results. This method can reduce the associated costs and eliminate unnecessary radiation exposure from medical scanning. However, depending on technique and operator, the quality and detail of the results can be more limited (Reichinger et al. 2013). The common benefit of all scanning approaches is that 3D modelling allows the 3D image of the typical ear to be superimposed with the microtia affected ear. This helps to determine the correct position

in relation to the patient's face and to help design the prostheses around the available tissue enabling a truly customised solution (Ciocca et al. 2007).

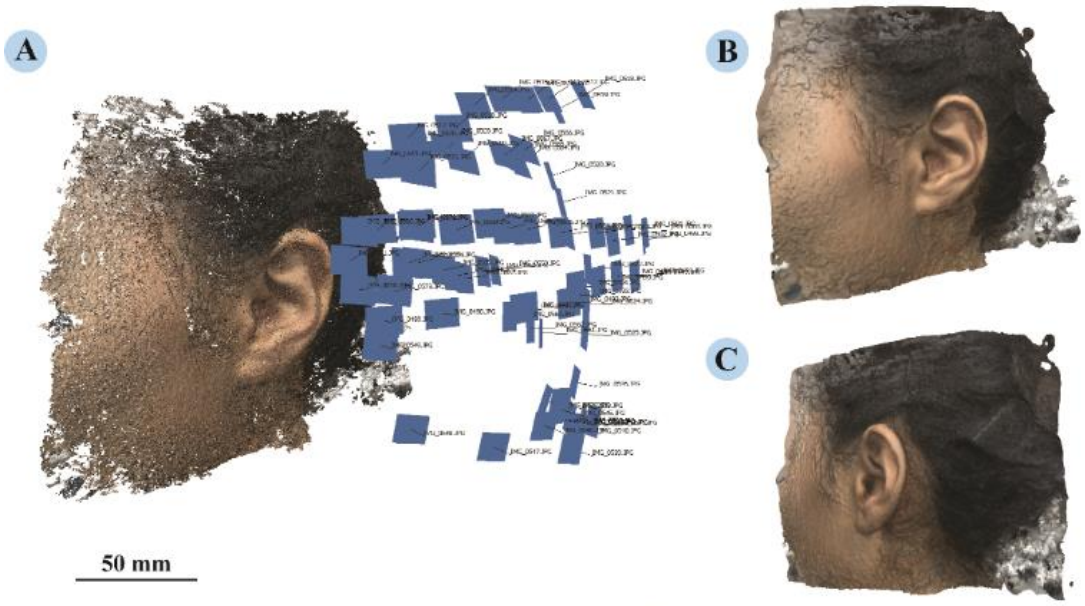

Figure 5. A 3D mesh created by photogrammetry using Agisoft Photoscan Standard Edition (Agisoft LLC, St. Petersburg, RUS) to process images taken with an iPhone 6 camera (Apple Inc., Cupertino, CA, USA). A) Dense point cloud computed by observing common features in the photo set - each blue square represents the positions where each photo was taken in 3D space as estimated by the program; B) and C) show the resulting completed 3D model of the mesh as computed from the dense point cloud with B) showing the 3D model from the front and C) showing the 3D model from the back.

Indirect 3D printing

3D manufacturing can be effectively applied in numerous stages of the manufacturing process for prostheses. Subtractive and additive manufacturing have been used to produce prototypes for the final prosthesis (Penkner et al. 1999, Subburaj et al. 2007, Watson and Hatamleh 2014) while other methods completely eliminate the prototype phase, using additive

manufacturing to fabricate a mould for the final prosthesis (Figure 6) (Ciocca et al. 2007, Liacouras et al. 2011, He et al. 2014). Eggbeer et al. (2012) compared both methods for the fabrication of a nasal prosthesis. Their study suggested that the best method was to 3D print a negative mould of the prosthesis rather than 3D printing the prosthesis itself. They suggest that there is an advantage to 3D printing the mould and then casting the silicone over directly 3D printing the silicone prosthesis. This is because direct 3D printing silicone compromises the material properties of the silicone during manufacturing with current silicone 3D printing technologies. They also noted that the time for fabrication was considerably shorter than conventional methods (Eggbeer et al. 2012). A number of case studies have used rapid prototyping to fabricate a master ear based on patient scans which was then used to make a prosthesis using the traditional methods but eliminating the need to take impressions from the patient directly. This, however, remained a time intensive process.

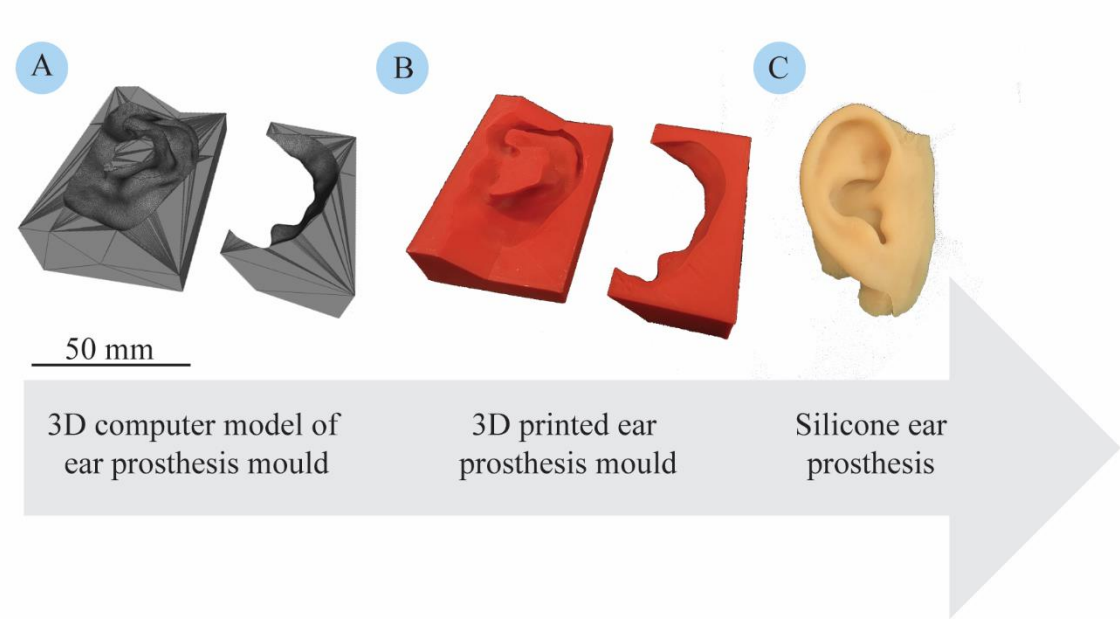

Figure 6. Schematic of indirect 3D printing of ear prostheses: A) 3D computer model of an inverse mould of the ear; B) 3D printed inverse mould printed using a fused deposition modelling (FDM) printer; C) final cured silicone ear prostheses.

The 3D printers used in the aforementioned processes were often 3D powder printers (Zprinters) (Ciocca et al. 2007, Liacouras et al. 2011, Watson and Hatamleh 2014) or industrial-grade fused deposition modelling (FDM) printers (Subburaj et al. 2007, He et al. 2014, Eggbeer et al. 2012). These printers are capable of producing very high quality 3D models with a smooth finish due to their very high layer resolution, however, the machines themselves and associated materials are relatively high-cost. He et al. (2014) used a desktop, or "open source", 3D printer to lower the cost of making an auricular prosthesis. The lower layer resolution (hundreds of microns) of these desktop or open source 3D printers leads to a 'staircase effect' which is clearly visible. This, however, was shown to be reduced by using an acetone vapour technique. From this they were able to create a smooth, patient-specific prosthesis that could cost as little as US$29.10 (He et al. 2014). Whilst these studies have shown promising results for cost and time reductions in the fabrication process, increasing the automation of the process and decreasing the user skill may lead to even better outcomes, and considerable research efforts are being invested in this area.

Direct 3D Printing

The next step from 3D printing prosthetic moulds is to develop the methods and materials to directly 3D print the prostheses themselves. There exist commercially available printing materials marketed as "rubber-like" such as TangoPlus (Stratasys Ltd., Minnesota, US). Eggbeer et al. (2012) completed a comparison study on three different methods of fabricating a nasal prostheses: traditional with maxillofacial silicone; advanced manufactured mould with maxillofacial silicone and direct advanced manufactured with TangoPlus. Although aesthetically the prostheses all looked very similar, mechanical testing showed the TangoPlus prostheses had a tensile strength of one third of the maxillofacial silicone and a tear strength

of one fifth. Mohammed et al. (2017) printing a multi-layer ear prosthesis with varying compositions of TangoPlus to tailor skin pigmentation however, no mechanical testing was conducted. These studies indicate that direct printing with TangoPlus has limited application for the direct printing of prosthesis.

Research into materials development has looked at how maxillofacial silicones could be 3D printable. A novel two-part formulation of room-temperature vulcanising silicone has been developed for 3D printing (Jindal et al. 2016, Jindal et al. 2017). The best performing formulation had a hardness, tear strength and tensile strength within the range of current commercially available silicones. As early as 2013, Fripp Design (Fripp Design Ltd, London, United Kingdom), a research and development company, claimed to be 3D printing silicone. It wasn't until 2016 that a patent was granted. The technology claims to work by using two-part room temperature vulcanising silicone, comprising liquid silicone oil and a catalyst. The silicone oil is mixed with a thickener and cross linker and poured into a tank in the printer. A syringe needle is then inserted into the silicone oil and translated in the x, y and z axes while depositing the catalyst to build up the 3D silicone model in a layer-by-layer manner (Limited 2017). Although the direct printing of silicone has potential significant time and cost advantages over silicone casting into 3D printed moulds, current technologies such as that by Fripp Design suffer from highly visible layering due to the manufacturing method, which would be aesthetically undesirable in the context of a prosthetic. In principle these visible artifacts could be smoothed using post fabrication processing. However, the need for manual processing adds to the total prosthetic fabrication time reducing the advantages of direct silicone printing for this application. Given the natural progression of 3D printing technologies in terms of layer resolution and accuracy, it is feasible that with further development direct printing of silicone prosthetics will be viable in the near future.

Biofabrication

3D printing is not limited to production of removable prostheses; research across the globe shows its successful application to permanent implants and tissue engineering. Biofabrication is the term used to describe the use of this technology to 3D print biomaterial constructs containing biological material (Paxton et al. 2016). Since the 1990's tissue engineering has been explored as an alternative to autologous reconstruction (Cao et al. 1997). Recent methods investigate the use of biofabrication to fabricate ear shaped scaffolds by moulding or direct 3D printing biomaterials (either synthetic polymers, hydrogels or a composite of these). Such scaffolds can be used for customised tissue regeneration by seeding with chondrocyte cells and relevant growth factors (Nayyer et al. 2012). The greatest challenge of this research is in creating the ideal environment to encourage the proliferation of cells whilst maintaining the large and complex structure of the ear. A potential solution to this limitation is through the use of hydrogels which have been shown as excellent materials for supporting the formation of neocartilage (Figure 8A) (Reiffel et al. 2013, Cohen et al. 2016). Cohen et al. (2016) showed the potential for collagen hydrogels to form the desired shape and environment for the long term development of auricular cartilage with native cartilage biochemical and mechanical properties either reached or maintained through the 6 months of the study. However, they observed contraction of the construct in the early stages of the study and they noted limited initial mechanical properties and were significantly less than native tissue. This was also observed by Shieh et al. (2004) who noted hydrogel only constructs tend to have relatively low tensile strength and fail to independently maintain their shape. Synthetic polymer materials like polyglycolic acid (PGA), poly-L-lactide (PLLA), and poly-caprolactone (PCL) have been investigated due to their mechanical properties however, they do not create the same hydrating environment and ideal matrix for cells as seen with hydrogels (Kusuhara et al. 2009).

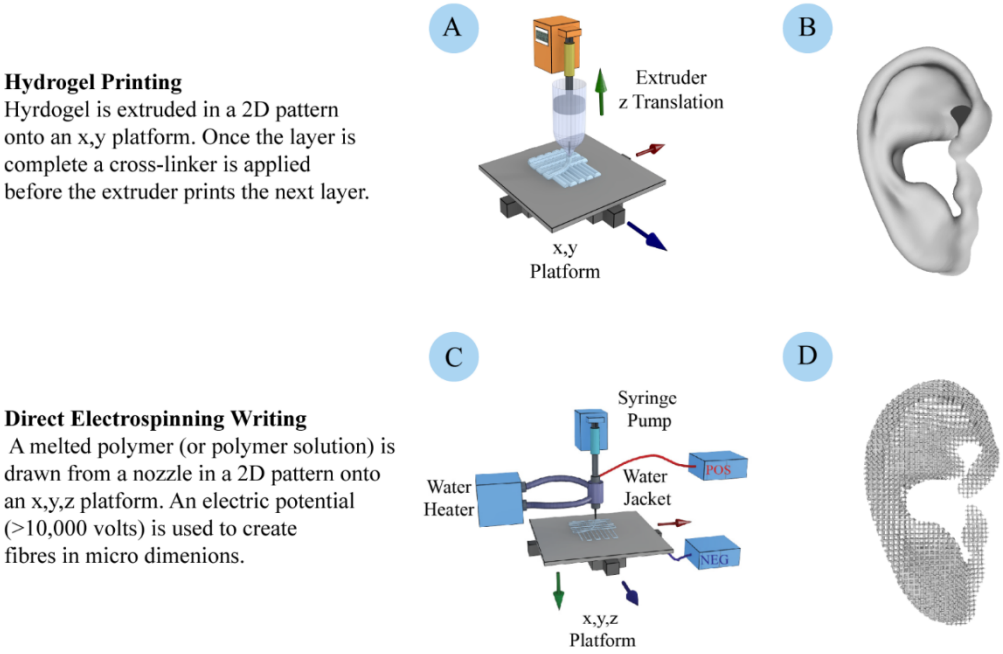

Figure 7. Schematic of 3D printing methods for fabricating personalised scaffolds for auricular cartilage regeneration. A) Hydrogels can be extruded in a controlled layer-by-layer manner to create scaffold structures using cross-linking, B) the ear shape scaffold can be seeded with chondrocytes to regenerate the cartilage tissue for reconstruction. C) Melt- or solution-electrospinning writing can be used to create polymer scaffolds with a fibre diameter that is in the tens of micron scale, D) these polymer scaffolds can be printed into personalised scaffolds for guiding tissue growth. Neither method has been fully optimised for regenerating auricular cartilage that maintains the complex shape of the ear. Perhaps used together, current research challenges could be overcome.

An emerging technique of 3D printing termed "melt-electrospinning writing" demonstrates even more potential for tissue engineering applications (Brown et al. 2011, Dalton et al. 2013, Wang et at. 2016). Melt-electrospinning is a method of 3D printing where a melted polymer is drawn from a syringe by a controlled electric field creating thin fibre

strands with diameters in the tens of micron scale, enabling scaffolds that "biomimic" the micro/nanostructures of tissue in the body (Figure 7). This method was developed following solution-electrospinning which required dissolving the polymer in solvents which had potential complications such as inflammation. A number of studies have shown that solution-electrospinning could provide a customised auricular framework suitable for microtia reconstruction (Xue et al. 2013, Walser et al. 2016). One solution electrospinning approach termed "electrohydro-dynamic jetting" demonstrated the ability to produce fibres with diameters ranging from 20μm to 200μm in ordered polycaprolactone scaffolds (Wang et at. 2016). With the advancements in these electrospinning approaches, it will be interesting to see their application to auricular cartilage scaffolds. Although these 3D biofabricated polymer scaffold approaches provide significantly improved mechanical properties over hydrogel only methods, they are limited in their provision of optimal biomechanical and biochemical environments for cell growth compared to hydrogels (Kusuhara et al. 2009). The limitations of scaffold only or hydrogel only fabrication approaches have been addressed through the development of novel composite material scaffolds that combine the strength and longevity of PGA, PLLA and PCL fibre scaffolds with the hydration and fibrous networks of hydrogels (Visser et al. 2013). Jung *et al.* (2016) developed a multiple-nozzle 3D printer capable of co-printing PCL and various alginate hydrogels in a layer-by-layer manner, selectively placing different gels within PCL framework (Figure 8B). It was found by Leong *et al.* (2016), that the surface modification of 3D PCL scaffolds by grafting glutaraldehyde through aminolysis significantly improved human dermal fibroblast infiltration over non-modified scaffolds. Park et al. (2016) demonstrated that printing alginate encapsulating modified chondrocytes (also termed bioinks) directly into PCL scaffolds resulted in improved cell viability and chondrocyte functionality for cartilage regeneration in a rabbit ear compared to PCL scaffolds that were cell-seeded via a modified chondrocyte suspension. Kang et al. (2016) have taken

this further, exploring the use of a multiple cartridge printer to fabricate tissue constructs by direct printing PCL and bioinks together in a layer by layer approach. The study showed the feasibility of printing human sized auricles out of PCL and a cell laden composite hydrogel that generated cartilage with properties similar to native tissue (Figure 8E). A similar study by Heo et al. (2017) combined a biodegradable polymer (polyactic acid) for the 3D printed scaffold structure and reinforced it with photo-curable gelatin hydrogels incorporating gold nanoparticles and human adipose-derived stem cells (ADSC). They showed the gelatin reinforced 3D printed structure can be tailored to have comparable mechanical stiffness to natural tissue and the ADSC's remained viable throughout their in vitro study. Although these works demonstrated the potential for composite materials in the biofabrication of personalised ear constructs, with the advantages of the mechanical strength of supporting polymer scaffolds containing cell-laden hydrogels, the extrusion melt printing (fused deposition modelling) of the polymer is limited to producing a relatively large polymer fibre diameter (in the order of hundreds of microns). This is much thicker than fibres produced using electrospinning techniques, which can fabricate fibres that are only microns thick. The fibre thickness determines the number of layers that are 3D printed for a given construct thickness and thereby the printing resolution. This is important because fibre thickness impacts the surface area to volume ratio for a given porosity, potentially important for surface availability for cell attachment. To address these fibre thickness limitations of FDM polymer fibre-reinforced scaffolds, Visser et al. (2015) produced melt-electrospun fibre reinforced hydrogels which shows promise as a technique to address the limitations of FDM polymer fibre reinforced scaffolds, demonstrating ordered microfibre reinforced hydrogels provides increased stiffness with the elasticity and stiffness close to that of articular cartilage. A micrograph of this work is shown in Figure 8D. The other component of the outer ear is skin. Current surgical processes involve the use of the patients existing skin above their ear location

(temporoparietal fascia), which is stretched over the cartilage framework during surgery. Direct bioprinting of skin, using microvalve-based and laser-based techniques, has been reviewed in Ng et al. (2016) and discusses the importance of several aspects of skin tissue engineering including control over pigmentation and the ability to produce vascular networks.

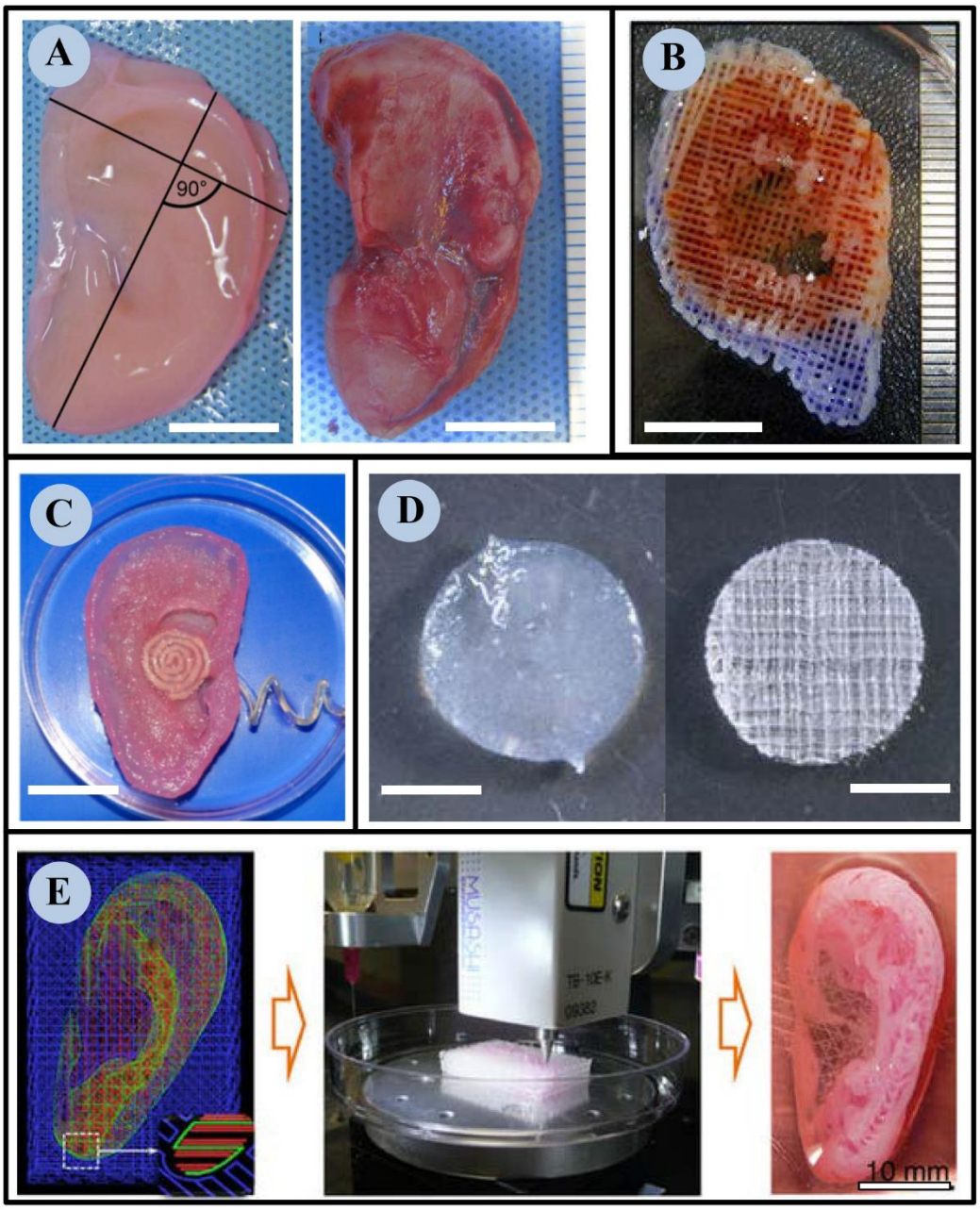

Figure 8. A) (left) Ear construct fabricated from collagen hydrogels set in moulds. Overlaid lines indicate the principal axes. (right) Cellular construct of bovine auricular chondrocytes in

collagen hydrogels explanted from a male athymic nude rat after 3 months. Scale bars = 10 mm. Reprinted with permission from Reiffel *et al.* (2013). B) 3D printed PCL scaffold in the shape of an ear. Alginate hydrogels selectively placed within PCL framework appearing blue and red, respectively. Scale bars = 10 mm. Reprinted with permission from Jung *et al.* (2016). C) 3D printed bionic ear consisting of a cell-seeded hydrogel matrix in the shape of a human ear containing an inductive coil antenna made from fused silver nanoparticles. Scale bars = 10 mm. Reprinted with permission from Mannoor *et al.* (2013) .Copyright 2013 American Chemical Society. D) Microscopy images of fibre-reinforced gelatin methacryloyl (GelMA) scaffolds. (left) GelMA gel and (right) melt-electrospun scaffold reinforced GelMA, ~93% porosity. Scale bars = 2 mm. Reprinted by permission from Macmillan Publishers Ltd: Nature Communications (Visser et al. 2015), Copyright 2015. E) (left) Software generates instructions for 3D scaffold/cell printer to build up ear construct. (middle) 3D printer extrudes polymer and deposits cell infused hydrogel. (right) The final ear shape is maintained by the polymer lattice containing the hydrogel. Scale bar = 10mm. Reprinted by permission from Macmillan Publishers Ltd: Nature Biotechnology (Kang *et al.* 2016), Copyright 2015.

Future outlook

Whilst traditional methods provide suitable non-permanent and permanent treatment options for children born with microtia, and other auricular deformities, the literature shows a clear opportunity to further optimise these methods and patient outcomes. 3D photography, computer modelling and additive manufacturing can extensively shorten the process of making prostheses through eliminating the need to make impressions and hand sculpt moulds. Making this process more autonomous will significantly reduce the cost to patients as well as making it easier to replace prostheses after their average two year life span. These techniques have also been shown to have promising outcomes when adapted to developing new tissue

engineered approaches to surgical construction. 3D printing implantable scaffolds from biomaterials and bioinks would eliminate tissue harvesting and donor site morbidity, improve customisation and if successful, remove the risks of foreign body complications seen with alloplasty. With personalised solutions being increasingly demanded, 3D printing and biofabrication technologies are poised to have a significant impact on many areas of traditional manufacturing worldwide. Their medical applications have the potential to influence numerous traditional treatment options for better health outcomes, cost-effective solutions and new skills and jobs emerging in the clinical space. 3D printing technology is also capable of fabricating functional electronics. Although in the early stages of development, the ability to interweave functional electronics with biological tissue would enable bionic organs to be fabricated with enhanced functionalities over natural capabilities. As shown in Figure 8C, Manu et al. (2013) produced a 3D printed bionic ear consisting of a cell-seeded hydrogel matrix formed in the morphology of a human ear and entwined a conducting polymer of fused silver nanoparticles which served as an inducting coil antenna. This enabled signal readout of inductively-coupled signals from electrodes shaped like the cochlea.

Additive manufacturing technologies such as 3D printing and biofabrication have the potential to improve both the production of customised, highly realistic, prosthetic ears, and the 3D printing of "living" ear constructs for surgical implantation incorporating the patient's own cells. The key advantages of 3D printing over traditional approaches for the production of prosthetic ears are; the reduced need for a highly skilled prostheticist to produce silicone ears, the ability to obtain the morphology of patient's ear geometry using non-invasive optical scanning as opposed to direct contact methods for obtaining a physical cast of the ear, the use of 3D computer modelling to rapidly produce a precise digital model of the required

prosthetic ear, and the ability to rapidly 3D print several low-cost, accurate, and personalised silicone prosthetic ears in an automated manner as required by the patient.

The key advantage of 3D printing over traditional surgical techniques is its ability to produce a personalised and accurate biofabricated ear using the patient's own cells. This is without the need to hand-craft the cartilage framework harvested from the patient's own rib cartilage (with associated donor site morbidity) or to use permanent polyurethane implants that have limited customisability and can suffer failure. Many of the leading biofabrication approaches use biodegradable polymer scaffolds that are fabricated into the precise shape of the patient's ears. The patient's own cells are then printed into the scaffold and allowed to proliferate prior to implantation, after which the polymer safely degrades away over time. The use of 3D digital technologies will revolutionise the treatment of microtia and other conditions with the ability to rapidly produce highly personalised solutions in an automated fashion without the need for highly skilled prostheticists and surgeons. This has the potential for improved clinical and aesthetic outcomes over traditional methods while reducing the costs and thereby improving access to the best treatments.

Acknowledgements

MTR would like to thank Advance Queensland for their support of this work through the Knowledge Transfer Partnership. The authors of this study would also like to gratefully acknowledge the contribution of Matthew Lanaro and Mathilde Desselle.

Conflict of interest

There are no conflicts of interest the authors need to disclose.

Funding

There are no funding sources for this work that the authors need to disclose.

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Glossary

alloplastic	Metal, ceramic, and plastic and other non-biological material
anotia	The congenital absence of the either one or both ears.
atelectasis	The collapse of one or all lung tissue of one lung.
atresia	The congenital closure or absence of an opening or tubular structure
auricle	Also called the pinna, the auricle is the projecting section of the ear that is outside the head
autogenous	Origin is from within the body tissue. e.g. cells from the affected person.
autograft	See autologous graft
autologous graft	A graft that is taken from a region of the patient's own body during surgery.
biomimic	Engineered imitation of biological processes or designs.
cartilage	Fibrous connective tissue with a specialised function; hyaline cartilage, fibrocartilage and elastic cartilage.
chondrocyte	A cell embedded within in cartilage matrix
fibroadipose	Tissue containing both fatty and fibrous structures.
hydrogel	A gel-like colloidal material where the particles are in the dispersion or external phase and water is in the dispersed or internal phase.

maxillofacial	Region of the body related to the jaws and face with reference to specialised surgery of this region.
morbidity	A diseased condition or state.
neocartilage	Cartilage grafts cultured in vitro produced from chondrocytes and used to treat defects of the joint and other cartilage regions.
osseointegration	Attachment to the bone of alloplastic inert material that has no connective tissue intervening.
pneumothorax	Air or gas collected in the chest resulting in the collapse of all or part of a lung.
subdermal	Beneath the skin.
temporoparietal fascia	Fibrous layer of tissue covering the temporalis muscle.
vascular	Relating to blood vessels and/or blood supply.