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Three-Dimensional Printing in Cleft Care: A Systematic Review

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Abstract

Objective: To determine the current applications of 3-dimensional (3D) printing in the care of patients with cleft lip and palate. We also reviewed 3D printing limitations, financial analysis, and future implications.

Design: Retrospective systematic review.

Methods: Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were used by 3 independent reviewers. Articles were identified from Cochrane library, Ovid Medline, and Embase. Search terms included 3D printing, 3 dimensional printing, additive manufacturing, rapid prototyping, cleft lip, and cleft palate. Exclusion criteria included articles not in English, animal studies, reviews without original data, oral presentations, abstracts, opinion pieces, and articles without relevance to 3D printing or cleft lip and palate.

Main Outcome Measures: Primary outcome measure was the purpose of 3D printing in the care of patients with cleft lip and palate. Secondary outcome measures were cost analysis and clinical outcomes.

Results: Eight-four articles were identified, and 39 met inclusion/exclusion criteria. Eleven studies used 3D printing models for nasoalveolar molding. Patient-specific implants were developed via 3D printing in 6 articles. Surgical planning was conducted via 3D printing in 8 studies. Eight articles utilized 3D printing for anatomic models/educational purposes. 3-Dimensional printed models were used for surgical simulation/training in 6 articles. Bioprinting was utilized in 4 studies. Secondary outcome of cost was addressed in 8 articles.

Conclusion: 3-Dimensional printing for the care of patients with cleft lip and palate has several applications. Potential advantages of utilizing this technology are demonstrated; however, literature is largely descriptive in nature with few clinical outcome measures. Future direction should be aimed at standardized reporting to include clinical outcomes, cost, material, printing method, and results.

Keywords

3-dimensional printing, cleft lip, cleft palate, nasoalveolar molding, bioprinting, surgical training, anatomic model, surgical simulation, patient-specific implants, patient education

Introduction

Cleft lip and cleft palate affects 1 in 1000 infants in the United States (Mai et al., 2019). Timely reconstruction of these malformations is of utmost importance due to the impact on feeding, speech, facial growth, and cosmesis (Nahai et al., 2005). However, repair requires a technically demanding operation and an intimate understanding of the anatomical presentations of both cleft lip and cleft palate. In addition, repair necessitates patient and family education of a complex cosmetic and functional deficit.

The advent of 3-dimensional (3D) printing has been widely recognized across surgical specialties. Use of this technology

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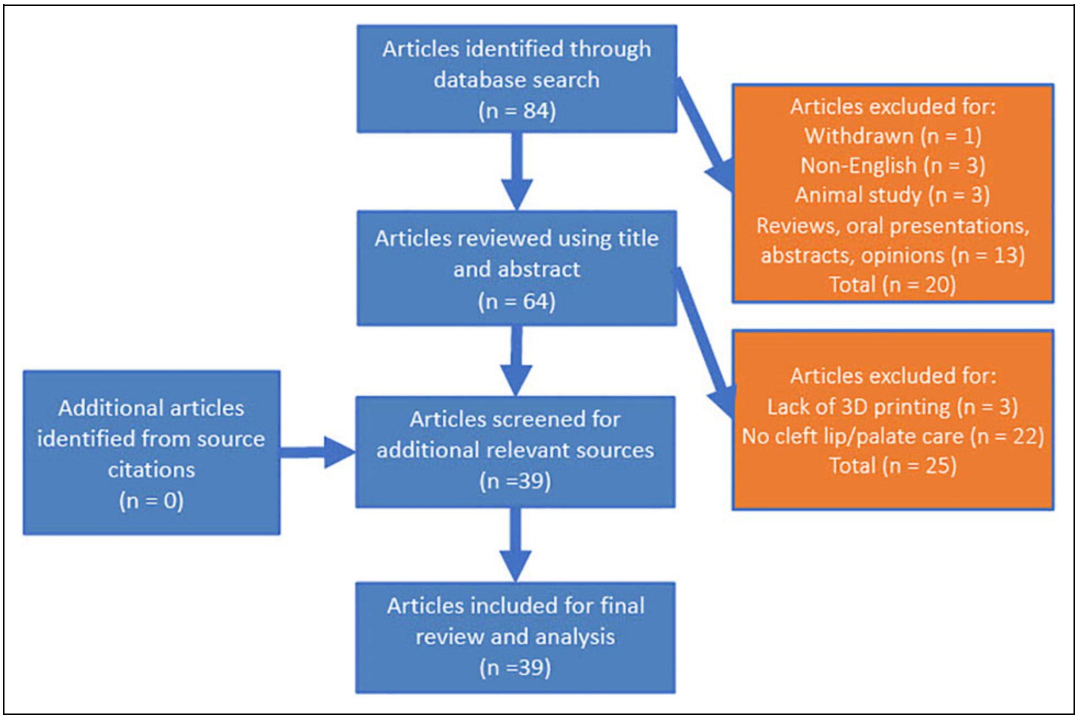

Figure 1. PRISMA flowchart. PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-analyses.

within the field of facial plastics and reconstructive surgery is rapidly expanding (Hsieh et al., 2017). Several reports address a wide array of methodologies of use, applications, cost, and clinical outcomes (Hsieh et al., 2017). However, the literature has been limited in scope, random in application, and case-specific due to its personalized nature (Hsieh et al., 2017). In addition, the variety of printers, materials, processes, and protocols make for an amalgam of information that can be difficult to digest for clinicians hoping to utilize this technology.

Our objective is to systematically review the use of 3D printing in cleft lip and palate care, with an emphasis on current uses, clinical outcomes, and financial analysis. We also hope to identify the limitations of 3D printing and recognize the future implications of this technology for the care of these patients.

Methodology

Three independent reviewers conducted a systematic review using Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Articles were identified from Cochrane Library, Ovid Medline, and Embase without chronologic limitations. Search terms included 3D printing, 3 dimensional printing, additive manufacturing, rapid prototyping, cleft lip, and cleft palate. Exclusion criteria included articles that were not in English, animal studies, reviews without original data, oral presentations and abstracts, opinion pieces, and articles without relevance to 3D printing or cleft lip and palate. Additional articles were screened for source citations. Level of evidence was determined based on the modified Oxford Centre for Evidence-Based Medicine 2011.

Results

Eight-four unique articles were identified, and 39 articles were included after applying inclusion and exclusion criteria (Figure 1). The majority of articles are of level IV or V evidence (79.5%). Our primary outcome was the purpose of 3D printing for cleft lip and cleft palate care. The literature was evaluated for advantages provided by 3D printing relative to traditional methods. Identification of cost analysis and clinical outcomes were reviewed as secondary outcomes. Articles are summarized in Table 1.

The articles included were divided into 6 main categories based on application: Nasoalveolar molding (NAM), patient-specific implants (PSI), bioprinting, surgical planning, surgical simulation/training, and for education or anatomic models. Patient-specific implants are distinguished as a category by a 3D-printed construct implanted for cleft-related care, not otherwise used for NAM or bioprinting. For the purpose of this review, the definition of bioprinting was broadened to include literature that followed the principles of tissue engineering to create bioactive structures for the care of patients with cleft lip and/or palate. Articles included in the category of surgical planning utilized 3D printing technology to aid in preparation for or intraoperative assessment of cleft-related surgery. This is differentiated from articles that utilized the technology for surgical simulation/training as the latter was not patient-

Table 1. Publications Relevant to 3D Printing in Cleft.

Source	Application type	LOE	Printer/printing method	Materials	Outcomes	Cost analysis
Yu et al. (2011)	NAM	4	Not stated	Not stated	3D imaging-based NAM technique for an accurate and reliable digital denture model using computer-aided reverse engineering.	None
Gong and Yu (2012)	NAM	4	Not stated	Not stated	Digital system for designing and producing NAM therapy. Simplify reconstruction procedures and decrease clinic adjustment time.	None
Shen (2015)	NAM	4	Not stated	Acrylic resin	Nasoalveolar molding protocol to improve presurgical cleft characteristics, while decreasing the burden on patients, families, and clinicians.	None
Ritschl (2016)	NAM	2	Scan-LED technology	Methacrylate-based material (Innovation MediTech GmbH)	NAM plates produced virtually using CAD/CAM technology with no significant difference from conventional technique.	None
Zheng (2016)	NAM	5	AFS-360 (SLS)	PSB-1 (polystyrene powder)	Development of a simple and effective CAD/CAM method for nasal molding.	None
Grill et al. (2018)	NAM	2	Not stated	Acrylic resin	Rapid NAM overcomes previous limitations of conventional CAD/CAM-intraoral molding plates by its semiautomated workflow.	Yes RapidNAM: $155 before extra costs $66-$103.
Grill et al. (2018)	NAM	2	Not stated	Orthorcyl® acrylic resin	The quick-lock system of CAD/CAM-NAM devices is time-efficient and reduces treatment hours.	None
Ahmed et al. (2019)	NAM	5	FDM, digital light processing, SLS	Different polymers of plastics, methyl methacrylate (MMA), and polymethylmethacrylate	Workflow process to predictably fabricate NAM devices using SLA printing which is cost-effective and accurate.	None
Batra (2019)	NAM	4	Eden 500 (Polyjet)	Opaque resin MED620, OrthoAligner Ultimate	One of the world's first documented cases of PSIO treated with a series of clear aligners.	None
Schiebl et al. (2019)	NAM	4	Fab-13 printer	GR-10 resin (Pro3dure)	Algorithm generates 3D-printable series of NAM device designs reliably.	None
Zheng et al. (2019)	NAM	5	Micro Plus 3D printer (fused filament fabrication)	Acrylic resin (Vertex-Dental)	Split-type 3D-printed PNAM for management of unilateral CLP.	None
Wu et al. (2017)	PSI	4	Connex3 (Polyjet)	Photosensitive polymer powder, hydroxyapatite (HA)	Customized implant materials overcoming limitations of ready-made materials and improving reconstruction of the defected pyriform aperture.	None
Boyer et al. (2018)	PSI	5	MakerBot Replicator (FDM)	Polylactic acid (PLA)	Hollow nasal supports with high level of contour replication and antibiotic coating for *E coli* inhibition	None
Krey et al. (2018)	PSI	4	Digital light processing (DLP)	Class IIa biocompatible material (Shera print-ortho plus)	Risk-free digital impression with subsequent digitally constructed and 3D-printed palatal plate.	None
Luo (2018)	PSI	5	Form labs 2 (SLA)	Dental SG resin cartridge	Design and printing of personalized nasal stents for cleft lip using 3D technology.	None

(continued)

Table 1. (continued)

Source	Application type	LOE	Printer/printing method	Materials	Outcomes	Cost analysis
Visscher (2018)	PSI Surgical planning/ volumetric analysis	4	Zprinter 250 (Inkjet)	Not stated	MRI is a repeatable and valid imaging modality to produce alar constructs for patient-specific reconstruction.	None
Pettersson et al. (2019)	PSI Surgical planning/ volumetric analysis	5	Vat photopolymerization, material jetting, binder jetting, material extrusion, powder bed fusion, direct energy deposition	Not stated	In Finland 2016-2017, additive manufacturing is routinely used in the head area at university hospitals.	None
Palhazi et al. (2014)	Surgical planning/ volumetric analysis	5	Objet30 Pro (PolyJet)	Objet Rigid White Material	A reproducible, step-by-step planning method; manual rather than automatic.	None
Du et al. (2017)	Surgical planning/ volumetric analysis	3	Zprinter 350 (Multijet)	None	Accurate estimation of graft volume in alveolar cleft patients can be performed by 3D-printed models as well as CAE software.	None
Kasaven et al. (2017)	Surgical planning/ volumetric analysis	3	Dimension 1200es (FDM)	White P430 ABSplus plastic	Virtual and printed 3D models as precise as the validated computer algorithm for alveolar cleft volumes, with virtual models being the most accurate.	None
Nicot et al. (2018)	Surgical planning/ volumetric analysis Educational/ anatomic Model	5	UPplus2 (FDM)	Acrylonitrile-butadiene-styrene (ABS)	SROP haptic model for accurate preoperative planning and better prenatal information for parents.	None
Chou et al. (2019)	Surgical planning/ volumetric analysis	3	Objet30 OrthoDesk (Polyjet)	Biocompatible photopolymer material (MED610), Synthetic modeling clay	Alveolar cleft defect volumes quantifiable by 3D-printed and virtual simulation methods for planning and surgery.	None
Chen (2019)	Surgical planning/ volumetric analysis	3	Massportal XD30 (fused filament fabrication)	Not stated	Two accurate volumetric methods for assessing bilateral alveolar clefts using 3D-printed models or CAE software.	None
Zheng et al. (2015)	Sugical simulation and training	5	AFS-360 (SLS)	Wax, silicone	Surgical trainees practiced the basic skills of cheiloplasty on the simulator and proved its worth.	Yes $50/model
Ueda et al. (2017)	Surgical simulation and training	5	Inkjet	Polyurethane from polyols (70%) and isocyanate (30%)	Two-layer elastic models for realistic simulated flaps for cheiloplasty.	Yes Face and cleft lip models: $61 and $33 respectively.
Podolsky et al. (2018)	Surgical simulation and training	5	Not stated	Multilayered soft tissues, bone, and realistic dissection planes	Simulator is realistic and valuable tool for training in cleft lip surgery.	Yes $250 per cleft lip stimulator cartridges
Choi and Shin (2019)	Surgical simulation and training	4	J750 (Polyjet)	Polyjet Tango Plus and Vero White Plus (Stratasys)	Intraoral scanner as a novel diagnostic tool for recording 3D data in patients with cleft palate for surgical planning, models, and training.	None

(continued)

Table 1. (continued)

Source	Application type	LOE	Printer/printing method	Materials	Outcomes	Cost analysis
Reighard et al. (2019)	Surgical simulation and training	4	Not stated	Polylactic acid (PLA), dyed silicone	High-fidelity, low-cost educational tool for trainees.	Yes Reusable molding system: \$11.43; consumable cleft lip model: \$4.59
Calonge et al. (2016)	Educational/ anatomic model	5	Formlabs (SLA and SLS)	Liquid white photopolymer resin (mixture of methacrylate monomers, methacrylate oligomers, and photoinitiator)	Free downloadable template for 3D printed cleft lip models for learning and surgical training.	None
Lioufas et al. (2016)	Educational/ anatomic model	4	Z650 Printer (Binder jet/powder), Projet 4500, ConnexJ750 (Polyjet)	Hard plastics mixed with rubber like Tango plus	3D printed models of cleft palate deformities using MRI scans. Prototype 3D replica with a soft, deformational material for use as a training model.	Yes Complete heads: Aus\$210-\$258; Cropped soft-palate model: Aus\$59.
AlAli et al. (2018)	Educational/ anatomic model	3	Formlabs1 (SLA)	Photoreactive resin White SDS	Effectiveness of 3D models as educational tool to aid imaging interpretation, resulting in improved student knowledge and satisfaction.	Yes \$32/model, \$322 per liter for resin
Chou et al. (2018)	Educational/ anatomic model	4	Fortus (FDM), Connex (Polyjet)	ABS plastic (solid), TangoPlus (soft tissue)	3D-printed models of cleft conditions that have a useful role in patient, parental, and allied health education.	None
Cote et al. (2018)	Educational/ anatomic Model Surgical simulation and training	4	Ultramaker 2+ (fused filament fabrication)	Polylactic acid (PLA)	Portable and low-cost 3D-printed realistic models for teaching and learning cleft palate repair techniques.	Yes \$7.31/model
Coté et al. (2018)	Educational/ anatomic models	4	Ultramaker 2+ (fused filament fabrication)	Polylactic acid (PLA)	3D-printed models useful for education of the patients and positively affected maternal-fetal bonding.	None
Nicot et al. (2019)	Educational/ anatomic models	5	UPplus2® printer (FDM)	Acrylonitrile-butadiene-styrene (ABS)	3D-printed models showing craniofacial abnormalities for patient counseling and teaching activities.	None
Berger et al. (2015)	Bioprinting	4	Not stated	Tricalcium phosphate-polyhydroxybutyrate (TCP-PHB)	Scaffold-based tissue engineering as alternative for current gold standard of autologous bone grafts.	None
Hixon et al. (2017)	Bioprinting	5	Lulzbot TAZ 5 (FDM), Tissue scaffolding	Polylactic acid (PLA), CG cryogels	Cryogels customizable for patient-specific tissue engineering using 3D molds derived from CT.	None
Ahn et al. (2018)	Bioprinting	5	Micro-extrusion-based	Medical-grade PCL	Mesenchymal stem cells-seeded 3D-printed polycaprolactone scaffolds as promising alternative for alveolar cleft reconstruction.	None
de la Lastraa et al. (2018)	Bioprinting	4	Tissue scaffolding	Cryogel and hydrogel scaffolds	Cryogel scaffolds displayed ideal properties for bone reconstruction.	None

Abbreviations: CAD/CAM, computer-aided design/computer-aided manufacturing; CAE, computer-aided engineering; CLP, cleft lip and palate; CT, computed tomography; LED, light-emitting diode; LOE, level of evidence; FDM, fused deposition modeling; MRI, magnetic resonance imaging; NAM, nasoalveolar molding; SLS, selective laser sintering; PNAM, presurgical nasoalveolar molding; PSI, patient-specific implant; PSIO, presurgical infant orthopedics SLA, stereolithography; SLS, selective laser sintering; 3D, 3-dimensional.

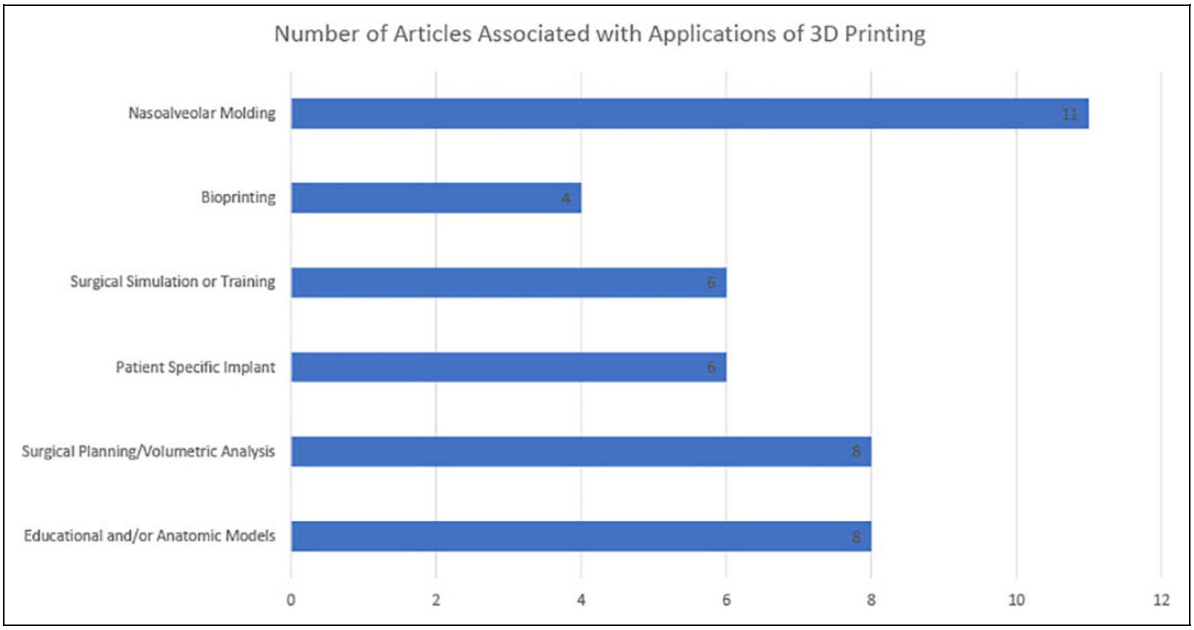

Figure 2. Number of articles associated with 3D printing in cleft lip and palate care by category. 3D indicates 3-dimensional.

specific and served to provide hands-on experience for development of surgical technique and competence. Finally, the educational/anatomic model category was separated from the reviewed literature as they were not used for surgical competence but for spatial understanding of anatomy for both trainees and patients.

Among the 39 articles included, 11 studies used 3D printing models for use in NAM. Patient-specific implants were developed via 3D printing in 6 articles. Bioprinting was utilized in 4 studies. Surgical planning with volumetric analysis and/or surgical guides was conducted via 3D printing in 8 studies. 3-Dimensional printed models were used for surgical simulation/training in 6 articles. Eight articles used 3D printing for anatomic models/educational purposes (Figure 2). Secondary outcome measure of cost analysis was identified in 8 articles. Clinical outcome measures were limited.

Discussion

The implications of 3D printing have been widely recognized in surgical specialties. With commercialization of technology and developments in material sciences, 3D printing demonstrates a trickle-down effect, leading to eventual standardization of its use in surgery. Specifically, application of this technology in the care of patients with cleft lip and/or cleft palate has numerous possibilities. Even so, the systematic review of this literature has identified a dearth of standardization in reporting outcomes, cost, and benefit to the patient and provider.

Nasoalveolar Molding

Nasoalveolar molding involves constructing a molding plate from a cast of the patient's maxilla, which is attached to a nasal stent. This is modified on a weekly or biweekly basis to "mold" the nasoalveolar defect nonsurgically in order to improve symmetry, project the nasal tip, elongate the columella, align the alveolar ridges, and decrease the gap between the cleft lip segments (Grayson et al., 1999; Grayson & Garfinkle, 2014). This complex, manual process of manipulating the patient molds requires high expertise, is time-consuming, and efficacy and efficiency of the treatment are dependent upon the practitioners' skills (Schiebl et al., 2019; Zheng et al., 2019).

Nasoalveolar molding is the most common utilization of 3D printing in cleft lip and palate care—11 studies were identified in this review. 3-Dimensional printing expedites the NAM process by reducing time, effort, and cost for both provider and patient (Yu et al., 2011; Schiebl et al., 2019; Zheng et al., 2019). Using scans of infant maxillary impressions, molds can be modified virtually and printed via additive manufacturing, creating multiple NAM devices at once after a single mold (Yu et al., 2011; Gong & Yu, 2012). Algorithms for semiautomated generation of NAM devices allow providers to generate multiple templates with a single initial mold. After virtual manipulation, this can be used to reliably 3D print NAM devices as measured by deviation between printed plate models and patient upper jaw models, effectively eliminating the need for manual manipulation by the clinician on a weekly basis (Schiebl et al., 2019). The clinical implications of streamlining NAM therapy with virtual planning and 3D printing include reducing frequency of appointments, decreasing the number of impressions/casts required, and minimizing the time-intensive manual adjustment of plates by the provider (Yu et al., 2011; Schiebl et al., 2019; Zheng et al., 2019). This is especially pertinent in the COVID-era health climate, allowing for continued care despite limitations to in-person visits.

Patient-Specific Implants

Use of 3D printing for clinical applications is almost universally patient-specific, creating a unique opportunity to efficiently personalize treatments. The use of 3D printing for PSI is distinguished by its use in cleft care that does not overlap with NAM or contain elements of bioprinting.

The6 articles identified using 3D printing for PSI focus on care of the cleft nasal deformity. The cleft nasal deformity creates multidimensional asymmetry producing a technically challenging and time-intensive repair (Wu et al., 2017). Moreover, existing methods for conforming the nose into a symmetric, aesthetically acceptable shape such as autograft cartilage or alloplastic materials do not match the shape of the defects even after surgeon modifications (Wu et al., 2017). 3-Dimensional printing offers an alternative that improves repair of pyriform aperture defects, alar reconstruction via 3D-printed silicon constructs, and personalized nasal stents postcleft lip repair or conformers postcleft rhinoplasty (Visscher et al., 2017; Wu et al., 2017; Boyer et al., 2018; Luo et al., 2019). This includes creation of custom nasal stents with increased level of contour replication, improved comfort and fit with resulting increased compliance (when compared to standardized conformers), all while improving nasal support and bypassing lengthy and complex production processes (Boyer et al., 2018; Luo et al., 2019). Luo et al. further discuss the needed technical competency, the different materials available for printing, and the level of software proficiency needed to make adjustments to the virtual model as the noncleft side that is mirrored is not always anatomically normal (Luo et al., 2019). Visscher et al. demonstrated high fidelity of the 3D-printed lateral crus to native cartilage for the purpose of reconstruction. This was performed reliably and quickly (segmentation of cartilage on imaging took approximately 7 minutes on average) via magnetic resonance imaging. The authors do suggest that for clinical application, there are limitations. Resolution of the imaging modality and the precision of the manufacturing process can result in a cumulative error in thickness of the implants being produced. The implication being the need for a high-resolution image with reliable 3D printing for an acceptable error of approximately 2 mm in thickness.

The applications to cleft care in the realm of PSI are not limited to nasal deformities. Krey et al. created a digital workflow and utilized 3D printing to produce presurgical palatal plates for infants with cleft palate (Krey et al., 2018). Ultimately, the use of 3D printing to produce PSI for cleft care has shown viable and translatable clinical results. Barrier to entry will be software and technological competency as the articles reviewed utilized different imaging processors to develop virtual 3D models for printing.

Bioprinting

Bioprinting uses 3D-printing technology to create cell-based scaffolds—live cells are part of the "bioink" used to print a 3D pattern to create the desired structure (Sears et al., 2016). Although the 4 articles included in this category do not use 3D printing to print cells, they use the principles of tissue engineering to create bioactive structures that are utilized in cleft care. The category was hence described as bioprinting to differentiate the work of these authors from the other uses of 3D printing in cleft care as described in this review.

In the present review, all 4 articles in this category used 3D printing to create acellular resorbable scaffolds. Each article demonstrated this for alveolar cleft reconstruction and overall bone regeneration for cleft defects. Currently, the gold standard for alveolar cleft osteoplasty utilizes autologous bone grafting. However, this creates an additional wound site with postoperative pain, scarring, and risk for infection. Further, it can be difficult to obtain sufficient marrow for grafting on pediatric patients and there remains a lack of specificity to the child/defect (Hixon et al., 2017; de la Lastra et al., 2018). The resorbable scaffolds produced in these studies were seeded with undifferentiated cell types with the goal of reducing or eliminating the morbidity associated with the current standard of care, while simultaneously providing a patient-specific repair (Berger et al., 2015; Hixon et al., 2017; Ahn et al., 2018; de la Lastra et al., 2018).

Bioprinting and tissue engineering in the medical field are in its infancy, and this is especially true in the case of cleft lip and palate care. Of the 4 articles included in the review, only 1 demonstrated the use of bioprinting in vivo via a case report of a 10-year-old patient (Ahn et al., 2018). At 6-month follow-up, the defect was noted to have "substantial amount of new bone" with lower mean density than surrounding bone. Comparison of this clinical outcome to the current gold standard was not available (Ahn et al., 2018). The remaining articles were in vitro studies.

This methodology will face several barriers as it evolves from scaffold implantation to live tissue printing. Regulatory bodies such as the US Food and Drug Administration may seek to encompass this technology into their scope of oversight as "cellular and tissue-based products," limiting the pace at which this reaches widespread applications (USFaD Administration, 2019). In addition, the articles also acknowledge the availability of current alternatives to and augmentation of the current gold standard of autologous bone grafting such as bone morphogenetic protein 2 (BMP-2), platelet-rich plasma, allografted bone, and deproteinized bovine bone—all with their own associated risks and benefits (Berger et al., 2015; Shakya & Kandalam, 2017). The technical barrier of harvesting undifferentiated stem cells to seed the bioactive scaffolds will further limit the widespread clinical utility of bioprinting in the care of patients with cleft lip and/or palate. Even so, the potential impact of developing protocols and operative techniques using bioprinting for the care of these patients holds tempered optimism as the field continues to expand.

Bioprinting is in its nascency as a technology with promising potential applications in the care of patients with cleft lip and palate. However, more reproducible and standardized processes will be required prior to its inclusion as standard practice.

Surgical Planning/Volumetric Analysis

In cleft lip and palate care, volumetric analysis of nasoalveolar cleft defects has largely been used for surgical planning. For these defects, iliac crest bone grafting stabilizes the maxilla by restoring continuity and preparing the maxilla for future orthodontic treatment (Jia et al., 2006; Du et al., 2017). Commonly, surgeons use intraoperative estimates from prior experience for autologous graft volumes rather than objective criteria (Chen et al., 2020). 3-Dimensional printing and virtual 3D modeling allow for nearly equally accurate and precise measurements of the defect volumes in patients with unilateral and bilateral cleft lip and palate (Du et al., 2017; Kasaven et al., 2017; Chou et al., 2019; Chen et al., 2020). Assessing the accurate volume of the alveolar defect may be helpful in surgical planning as it determines selection of donor site and contributes to the treatment outcome (Chou et al., 2019). In addition, volumetric analysis can guide the size of the iliac bone harvest, minimizing donor site morbidity and potential for iatrogenic complications such as pain, hematoma, pelvic instability, nerve injury, or poor cosmesis (Chou et al., 2019; Chen et al., 2020). Conversely, inadequate harvest risks failure in restoring the dental arch (Du et al., 2017).

Based on the reviewed literature, virtual 3D modeling provides a faster, more efficient, and potentially more accurate volumetric analysis than 3D-printed models (Chen et al., 2020). This is validated by comparison to 3D-printed models of alveolar clefts based on real patients as measured by volume of water displacement (Du et al., 2017; Kasaven et al., 2017; Chou et al., 2019; Chen et al., 2020). However, preoperative planning may be optimized with an actual 3D-printed model to provide haptic feedback and spatial understanding for the operating surgeon of how a graft can be inserted into the defect site (Palhazi et al., 2014; Chen et al., 2020). This would require upfront costs for both software and hardware, as well as manipulation of the virtual models manually resulting in additional time for preoperative planning (Palhazi et al., 2014). Unfortunately, a comparison in outcomes utilizing preoperative planning with 3D printing versus current standard of care is not available in the reviewed literature, nor the financials for the software and hardware utilized, making a cost-benefit analysis for the utilization of this technology challenging.

Although volumetric analysis is currently most readily used, surgical planning with 3D-printed models to guide surgical technique, creation of patient-specific surgical guides, and addressing complex cleft anomalies are on the horizon as the technology trickles down and becomes more cost-effective for institutional and single-surgeon use.

Surgical Simulation and Training

Developing the anatomic understanding and honing the numerous surgical techniques for cleft lip and palate repair presents its own set of challenges. Not only are the surgeries less common than other reconstructive surgeries, they are complex and require understanding of 3D anatomic malformations, evaluation of defects with various widths and sizes, and a feel for the fragility of the infantile tissues (Cote et al., 2018). A trainee must accomplish all of this with limited access to and visualization of the surgical site (Cote et al., 2018). In 1 study, operative times increased by 104% when trainees were involved in cleft lip and palate repair surgeries (Sasor et al., 2013). This increases the operative risks and monetary costs to the patient (Sasor et al., 2013). 3-Dimensional printing offers a solution by providing tactile models for surgical simulation and training. In this review, 6 articles utilized 3D printing to address surgical training in the care of patients with cleft lip and palate.

Cote et al. were guided by 3 criteria when approaching the development of a simulation model: easily manufactured, affordability, and anatomically correct (Cote et al., 2018). Prior to the mass availability of 3D printing, efforts to create surgical simulation through a variety of materials such as plastic mugs, balls, rubber bands, ink pads, and so on with different degrees of assembly had been attempted with varying success and utility (Vadodaria et al., 2007; Nagy & Mommaerts, 2009). In the reviewed literature, 3D-printed models of cleft lips and palates were created with different materials and assessed by both residents and attending surgeons for the models' physical attributes, ability to emulate the operative experience, and contribution to trainee education (Zheng et al., 2015; Ueda et al., 2017; Cote et al., 2018; Podolsky et al., 2018; Reighard et al., 2019). The models created allowed for accurate tactile sensation when incising with a scalpel, dissection and manipulation of tissue, and multilayer suturing (Zheng et al., 2015; Ueda et al., 2017; Cote et al., 2018; Podolsky et al., 2018; Reighard et al., 2019). Various surgical repairs were completed on these models including von Langenbeck palatoplasty, double opposing Z-plasty for palate repair, multiple styles of cheiloplasty, and primary cleft rhinoplasty (Zheng et al., 2015; Ueda et al., 2017; Cote et al., 2018; Podolsky et al., 2018; Choi & Shin, 2019; Reighard et al., 2019). Overall, the feedback received from those using the 3D-printed models for simulation was positive, relaying the notion that these models would be valuable assets in surgical training.

Future endeavors in supplementing surgical trainee education would benefit from a uniform approach to comparing the different materials available to 3D-print surgical models, both from a functional and cost perspective, as well as translation of the skills developed in the simulations to the operating room.

Educational/Anatomic Models

Three-dimensional evaluation of anatomy is a key principle in surgical education. Three-dimensional imaging and virtual reconstruction of 2-dimensional (2D) images into 3D constructs have mitigated this barrier to learning. 3-dimesional printed models of cleft lip and palate offer an opportunity to enhance anatomic education of students and residents.

Multiple studies have established the benefits of supplementing medical and surgical education with 3D-printed models for an improved learning experience (AlAli et al., 2018). In

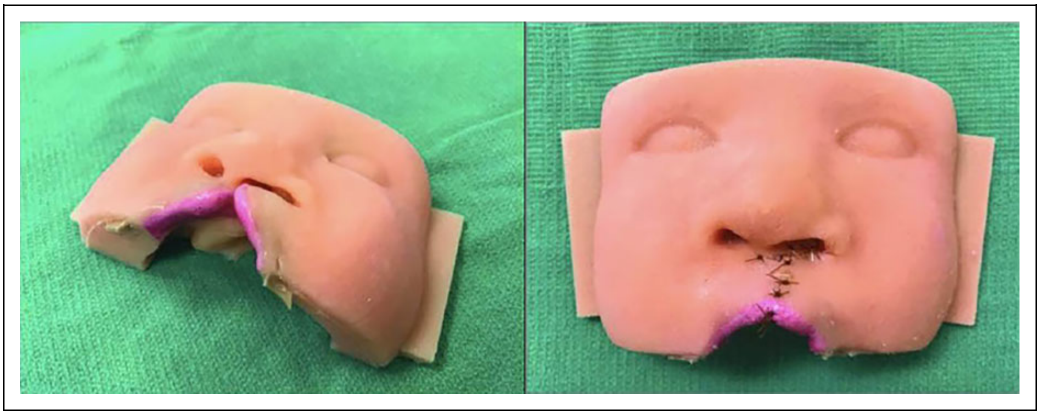

Figure 3. 3-Dimensional printed cleft lip simulator (Reighard et al., 2019).

1 study, a cohort of medical students were randomly split into 2 groups with the same lecture and lecturer. One of the groups also received a supplemental 3D model for the lecture. Based on a pre- and postlecture test, the study demonstrated a significant increase in "knowledge gained" due to utilization of the 3D-printed model (AlAli et al., 2018). With advancements in 3D-printing technology, models effectively replicate human anatomy with acceptable tissue likeness allowing for accurate and effective educational supplementation (Lioufas et al., 2016; Cote et al., 2018).

The educational uses of 3D-printed models are not limited to students and trainees—they can also be used as tools to augment the physician–patient/family interactions (Nicot et al., 2019). Even during the prenatal period, 2D ultrasound images converted into 3D-printed models have a positive impact on preparing parents and family for the birth of a child with a cleft lip and/or palate (Coté et al., 2018; Nicot et al., 2018; Nicot et al., 2019). This impact is seen via improved maternal bonding after delivery and on expectations for the multidisciplinary management required for the patient during childhood (Calonge et al., 2016; Coté et al., 2018). Chou et al. (2018) validated the utility of 3D-printed models for patient education by evaluating VAS surveys of parents of patients with cleft lip and/or palate. Their study questionnaires targeted parental perceptions of how well the models assisted their overall understanding of cleft lip and palate, velopharyngeal dysfunction and speech disorder, and alveolar bone deficiency (Chou et al., 2018). The findings demonstrated an overwhelmingly positive response for the utilization of 3D models in educating patient families on cleft lip and palate care (Chou et al., 2018).

Limitations of Current Literature

There is a growing body of literature describing the utility of 3D printing in the care of patients with cleft lip and palate. These applications are demonstrating real-world implications related to the use of 3D printing in several aspects of the care of these patients. However, there is an abundance of methods, processes, and workflows. Each have their own sets of costs and the literature is largely descriptive and anecdotal in nature.

Cost analysis. In this review, only 8 articles address cost of production of the 3D prints, and none review the upfront costs of acquiring the printers themselves. In a review of 3D printing in surgery, cost was a splitting factor among authors when determining whether it was worth the value added to patient care, with 24 authors believing the cost was overcome versus 30 believing it may be prohibitive (Martelli et al., 2016).

In regard to 3D printing specifically for the care of patients with cleft lip and palate, the cost-effectiveness may be more straightforward depending on its use. An implication explored by many of the articles reviewed for NAM was the cost-savings associated with reducing the time-intensive modeling required to create individual casts, the weekly patient visits, and the numerous molds that are needed from the patient's palate (Gong & Yu, 2012; Grill et al., 2018; Ahmed et al., 2019; Schiebl et al., 2019; Zheng et al., 2019). Grill et al. evaluated the cost-savings of conventional NAM molding plates (223 USD) compared to a semiautomated RapidNAM device (155 USD; Grill et al., 2018). Even so, this is representative of 1 protocol without specifics on the printer and materials used, making this difficult to reproduce. The remainder of the NAM literature using 3D printing provides no specific numbers nor a definitive cost analysis.

For the purposes of surgical training and simulation, there is more directly reported data. The high-fidelity cleft lip and palate simulators as seen in Figures 3–5 cost US$11.43, US$250, and US$7.31 to produce, respectively, representing the low and high-end ranges of costs reported for this application (Zheng et al., 2015; Ueda et al., 2017; Cote et al., 2018; Podolsky et al., 2018; Reighard et al., 2019). Two articles address the cost of educational or anatomic models. The model used by AlAli et al. as described above reported a cost of US$32 per model (AlAli et al., 2018). These uses appear to have costs that are amenable to widespread 3D-printing application. Although not reported, these costs are also likely to be translatable to 3D printing for surgical planning and volumetric analysis.

For these purposes, a secondary implication is the intraoperative time saved, decreasing both time under anesthesia for the patient and the cost of the operating room. In a review of 3D

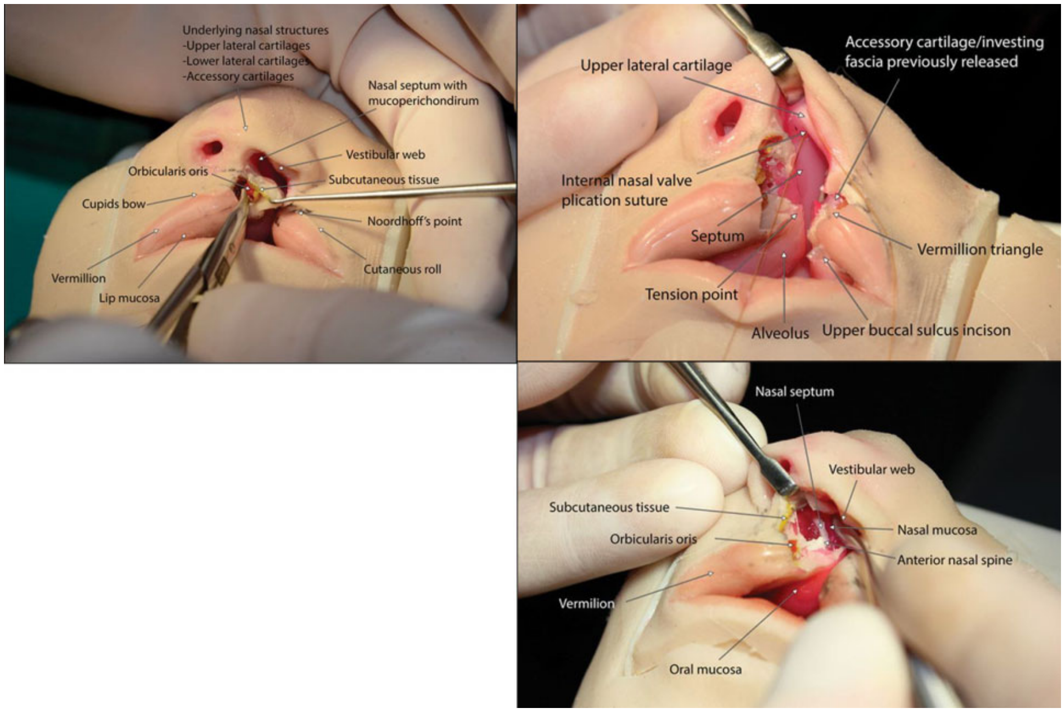

Figure 4. High fidelity 3D-printed cleft lip and nasal deformity simulator. Demonstrates distinct soft tissue and cartilaginous subunits and anatomic landmarks (Podolsky et al., 2018). 3D indicates 3-dimensional.

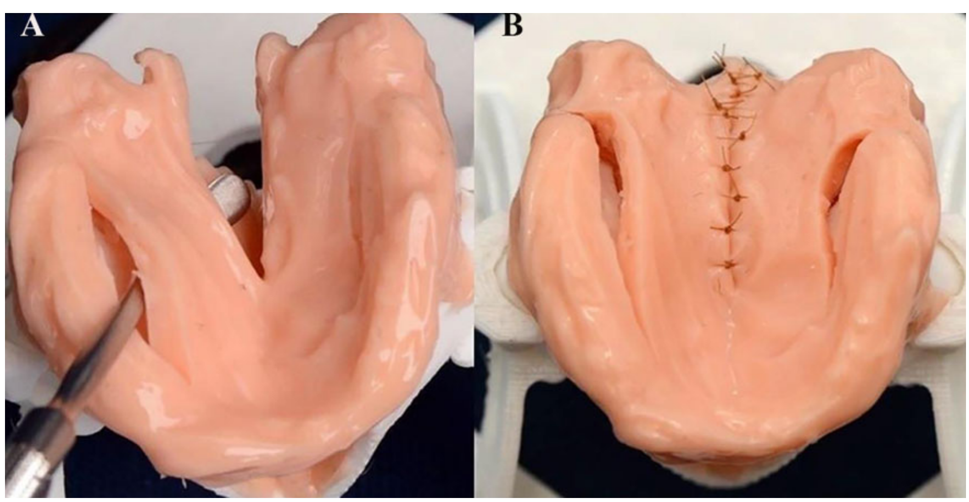

Figure 5. 3-Dimensional printed cleft palate simulation before and after von Langenbeck palatoplasty (Cote et al., 2018).

printing in surgery, not specific to cleft lip and palate, saved intraoperative time was reported in 52 articles, ranging from 5.7 to 63 minutes (Martelli et al., 2016). This may be especially true for cleft lip and palate operations where extensive intraoperative examination and planning often precedes actual instrumentation and repair.

Patient-specific implants and bioprinting both are very personalized uses of 3D printing. Thus, cost analysis for these is more difficult to obtain and less translatable. Bioprinting in particular has an incredibly high upfront cost as "bioprinter" and "bioink" cost is in the range of hundreds of thousands of dollars (O'Neill, 2020).

Overall, there is a dearth of cost analysis for 3D printing in the care of patients with cleft lip and palate. Although there are areas of utility that have reported costs amenable to widespread application of the technology (ie, NAM, surgical training and simulation, and educational models), there remains a lack of standardization, uniformity of protocol, and upfront cost barriers that may serve as hurdles to the reproducibility of these 3D-printing functions. Nevertheless, in an era of patient satisfaction-driven medicine, 3D printing can differentiate competitive providers, providing justification for the associated costs.

Level of evidence and clinical outcome measures. The majority of articles reviewed are of level IV and V evidence (Table 1). These studies are not only expansive in their breadth but also nonstandardized in their outcome measures, making a comparative review challenging. Numerous printers, different materials, lack of comprehensive cost analysis, and lower levels of evidence within the literature all contribute to the limitations in knowledge sharing and serve as a barrier to widespread application of 3D printing.

The personalized nature of 3D printing makes it particularly challenging to standardize. However, data with outcomes describing materials used, cost comparisons to traditional methods, and scenarios in which application of this technology is worthwhile with measurable clinical outcomes will help inform best practices in the field moving forward.

Another limitation not addressed by the articles included in this review is the technological barrier. Literacy in software utilization, programming, troubleshooting, and processing of printed products will require skill acquisition and implementation of new standard workflow processes for surgeons seeking to incorporate this into their practices. Nevertheless, the utilization of 3D printing for the care of patients with cleft lip and palate is low risk with high potential even without large-scale studies or randomized control trials for validation.

Conclusion

3-Dimesional printing applications for the care of patients with cleft lip and palate were found to be broad and provide potential value add in the areas of NAM, PSI, bioprinting, surgical planning, surgical simulation/training, and education. As impressive as the largely anecdotal applications of 3D-printing technology have been to the care of patients with cleft lip and palate, there remains a paucity of data, clinical outcome measures, and standardization of practices that can guide the future integration of this technology into the care of patients with cleft lip and palate.

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References

Administration USFaD. Tissue and tissue products. 2019. Updated January 27, 2021. Accessed September, 2020. https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products#:~:text=Human%20cells%20or%20tissue%20intended,based%20product%20or%20HCT%2FP.&text=One%20final%20rule%20requires%20firms,their%20HCT%2FPs%20with%20FDA.

Ahmed MK, Ahsanuddin S, Retrouvey JM, Koka KS, Qureshi H, Bui AH, Taub PJ. Fabrication of nasoalveolar molding devices for the treatment of cleft lip and palate, using stereolithography additive manufacturing processes and computer-aided design manipulation software. *J Craniofac Surg*. 2019;30(8):2604-2608.

Ahn G, Lee J-S, Yun W-S, Shim J-H, Lee U-L. Cleft alveolus reconstruction using a three-dimensional printed bioresorbable scaffold with human bone marrow cells. *J Craniofac Surg*. 2018;29(7):1880-1883.

AlAli AB, Griffin MF, Calonge WM, Butler PE. Evaluating the use of cleft lip and palate 3D-printed models as a teaching aid. *J Surg Educ*. 2018;75(1):200-208.

Batra P, Gribel BF, Abhinav BA, Arora A, Raghavan S. OrthoAligner "NAM": A case series of Presurgical Infant Orthopedics (PSIO) using clear aligners. *Cleft Palate Craniofac J*. 2020;57(5):646-655.

Berger M, Probst F, Schwartz C, Cornelsen M, Seitz H, Ehrenfeld M, Otto S. A concept for scaffold-based tissue engineering in alveolar cleft osteoplasty. *J Craniomaxillofac Surg*. 2015;43(6):830-836.

Boyer CJ, Woerner JE, Galea C, Gatlin CA, Ghali GE, Mills DK, Weisman JA, McGee DJ, Alexander JS. Personalized bioactive nasal supports for postoperative cleft rhinoplasty. *J Oral Maxillofac Surg*. 2018;76(7):1562. e1561-1562. e1565.

Calonge WM, AlAli AB, Griffin M, Butler PE. Three-dimensional printing of models of cleft lip and palate. *Plast Reconstr Surg Glob Open*. 2016;4(4):e689-e689.

Chen S, Liu B, Liu J, Yin N, Wang Y. Comparison of three-dimensional printing and computer-aided engineering in presurgical volumetric assessment of bilateral alveolar clefts. *J Craniofac Surg*. 2020;31(2):412-415.

Choi YS, Shin HS. Preoperative planning and simulation in patients with cleft palate using intraoral three-dimensional scanning and printing. *J Craniofac Surg*. 2019;30(7):2245-2248.

Chou P-Y, Denadai R, Hallac RR, Dumrongwongsiri S, Hsieh WC, Pai BC, Lo LJ. Comparative volume analysis of alveolar defects by 3D simulation. *J Clin Med*. 2019;8(9):1401.

Chou PY, Hallac RR, Shih E, Trieu J, Penumatcha A, Das P, Meyer CA, Seaward JR, Kane AA. 3D-printed models of cleft lip and palate for surgical training and patient education. *Cleft Palate Craniofac J*. 2018;55(3):323-327.

Coté JJ, Thomas B, Marvin J. Improved maternal bonding with the use of 3D-printed models in the setting of a facial cleft. *J 3D Print Med*. 2018;2(3):97-102.

Cote V, Schwartz M, Arbouin Vargas JF, Canfarotta M, Kavanagh KR, Hamdan U, Valdez TA. 3-Dimensional printed haptic simulation model to teach incomplete cleft palate surgery in an international setting. *Int J Pediatr Otorhinolaryngol*. 2018;113:292-297.

de la Lastra AA, Hixon KR, Aryan L, Banks AN, Lin AY, Hall AF, Sell SA. Tissue engineering scaffolds fabricated in dissolvable 3d-printed molds for patient-specific craniofacial bone regeneration. *J. Funct Biomater*. 2018;9(3):46.

Du F, Li B, Yin N, Cao Y, Wang Y. Volumetric analysis of alveolar bone defect using three-dimensional-printed models versus computer-aided engineering. *J Craniofac Surg*. 2017;28(2): 383-386.

Gong X, Yu Q. Correction of maxillary deformity in infants with bilateral cleft lip and palate using computer-assisted design. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012;114(5 suppl): S74-S78.

Grayson BH, Garfinkle JS. Early cleft management: the case for nasoalveolar molding. *Am J Orthod Dentofacial Orthop*. 2014; 145(2):134.

Grayson BH, Santiago PE, Brecht LE, Cutting CB. Presurgical nasoalveolar molding in infants with cleft lip and palate. *Cleft Palate Craniofac J*. 1999;36(6):486-498.

Grill FD, Ritschl LM, Bauer FX, Rau A, Gau D, Roth M, Eblenkamp M, Wolff K-D, Loeffelbein DJ. A semi-automated virtual workflow solution for the design and production of intraoral molding plates using additive manufacturing: the first clinical results of a pilot-study. *Sci Rep*. 2018;8(1):11845.

Hixon KR, Melvin AM, Lin AY, Hall AF, Sell SA. Cryogel scaffolds from patient-specific 3D-printed molds for personalized tissue-engineered bone regeneration in pediatric cleft-craniofacial defects. *J Biomater Appl*. 2017;32(5):598-611.

Hsieh T-Y, Dedhia R, Cervenka B, Tollefson TT. 3D Printing: current use in facial plastic and reconstructive surgery. *Curr Opin Otolaryngol Head Neck Surg*. 2017;25(4):291-299.

Jia YL, Fu MK, Ma L. Long-term outcome of secondary alveolar bone grafting in patients with various types of cleft. *Br J Oral Maxillofac Surg*. 2006;44(4):308-312.

Kasaven CP, McIntyre GT, Mossey PA. Accuracy of both virtual and printed 3-dimensional models for volumetric measurement of alveolar clefts before grafting with alveolar bone compared with a validated algorithm: a preliminary investigation. *Br J Oral Maxillofac Surg*. 2017;55(1):31-36.

Krey KF, Ratzmann A, Metelmann PH, Hartmann M, Ruge S, Kordass B. Fully digital workflow for presurgical orthodontic plate in cleft lip and palate patients. *Int J Comput Dent*. 2018;21(3):251-259.

Lioufas PA, Quayle MR, Leong JC, McMenamin PG. 3D printed models of cleft palate pathology for surgical education. *Plast Reconstr Surg Glob Open*. 2016;4(9):e1029-e1029.

Luo D, Li T, Wang H, Chen Y. Three-dimensional printing of personalized nasal stents for patients with cleft lip. *Cleft Palate Craniofac J*. 2019;56(4):521-524.

Mai CT, Isenburg JL, Canfield MA, Meyer RE, Correa A, Alverson CJ, Lupo PJ, Riehle-Colarusso T, Cho SJ, Aggarwal D, et al. National population-based estimates for major birth defects, 2010-2014. *Birth Defects Res*. 2019;111(18):1420-1435.

Martelli N, Serrano C, Brink H, Pineau J, Prognon P, Borget I, El Batti S. Advantages and disadvantages of 3-dimensional printing in surgery: a systematic review. *Surgery*. 2016;159(6): 1485-1500.

Nagy K, Mommaerts MY. Advanced S(t)imulator for cleft palate repair techniques. *Cleft Palate Craniofac J*. 2009;46(1):1-5.

Nahai FR, Williams JK, Burstein FD, Martin J, Thomas J. The management of cleft lip and palate: pathways for treatment and longitudinal assessment. *Semin Plast Surg*. 2005;19(4):275-285.

Nicot R, Couly G, Ferri J, Levaillant JM. Three-dimensional printed haptic model from a prenatal surface-rendered oropalatal sonographic view: a new tool in the surgical planning of cleft lip/palate. *Int J Oral Maxillofac Surg*. 2018;47(1):44-47.

Nicot R, Druelle C, Hurteloup E, Levaillant JM. Prenatal craniofacial abnormalities: from ultrasonography to three-dimensional printed models. *Ultrasound Obstet Gynecol*. 2019;54(6):835-836.

O'Neill B. 3D bioprinting: comprehensive guide and product selection. 2020. Updated January 11, 2021. Accessed September, 2020. https://www.aniwaa.com/buyers-guide/3d-printers/3d-bioprinting-3d-bioprinters/

Palhazi P, Nemes B, Swennen G, Nagy K. Three-dimensional simulation of the nasoalveolar cleft defect. *Cleft Palate Craniofac J*. 2014;51(5):593-596.

Pettersson ABV, Salmi M, Vallittu P, Serlo W, Tuomi J, Mäkitie AA. Main clinical use of additive manufacturing (three-dimensional printing) in Finland restricted to the head and neck area in 2016-2017. *Scand J Surg*. 2020;109(2):166-173.

Podolsky DJ, Wong Riff KW, Drake JM, Forrest CR, Fisher DM. A high fidelity cleft lip simulator. *Plast Reconstr Surg Glob Open*. 2018;6(9):e1871-e1871.

Reighard CL, Green K, Rooney DM, Zopf DA. Development of a novel, low-cost, high-fidelity cleft lip repair surgical simulator using computer-aided design and 3-dimensional printing. *JAMA Facial Plast Surg*. 2019;21(1):77-79.

Ritschl LM, Rau A, Güll FD, et al. Pitfalls and solutions in virtual design of nasoalveolar molding plates by using CAD/CAM technology—A preliminary clinical study. *Journal of Cranio-Maxillofacial Surgery*. 2016;44(4):453-459.

Sasor SE, Flores RL, Wooden WA, Tholpady S. The cost of intraoperative plastic surgery education. *J Surg Educ*. 2013;70(5):655-659.

Schiebl J, Bauer FX, Grill F, Loeffelbein DJ. RapidNAM: algorithm for the semi-automated generation of nasoalveolar molding device designs for the presurgical treatment of bilateral cleft lip and palate. *IEEE Trans Biomed Eng*. 2019;1-1.

Sears NA, Seshadri DR, Dhavalikar PS, Cosgriff-Hernandez E. A review of three-dimensional printing in tissue engineering. *Tissue Eng Part B Rev*. 2016;22(4):298-310.

Shakya AK, Kandalam U. Three-dimensional macroporous materials for tissue engineering of craniofacial bone. *Br J Oral Maxillofac Surg*. 2017;55(9):875-981.

Shen C, Yao CA, Magee W 3rd, Chai G, Zhang Y. Presurgical nasoalveolar molding for cleft lip and palate: the application of digitally designed molds. *Plast Reconstr Surg*. 2015;135(6):1007e-1015e.

Ueda K, Shigemura Y, Otsuki Y, Fuse A, Mitsuno D. Three-dimensional computer-assisted two-layer elastic models of the face. *Plast Reconstr Surg*. 2017;140(5):983-986.

Vadodaria S, Watkin N, Thiessen F, Ponniah A. The first cleft palate simulator. *Plast Reconstr Surg*. 2007;120(1):259-326.

Visscher DO, van Eijnatten M, Liberton NPTJ, Wolff J, Hofman MBM, Helder MN, Don Griot JP, van Zuijlen PPM. MRI and additive manufacturing of nasal alar constructs for patient-specific reconstruction. *Sci Rep*. 2017;7:10021.

Wu Y, Wang G, Yang Y, Chen Y. Application of computer-aided design and customized implants in the reconstruction of pyriform aperture defects secondary to unilateral cleft lip and palate. *J Craniofac Surg*. 2017;28(6):1517-1520.

Yu Q, Gong X, Wang G-M, Yu Z-Y, Qian Y-F, Shen G. A novel technique for presurgical nasoalveolar molding using computer-aided reverse engineering and rapid prototyping. *J Craniofac Surg*. 2011;22(1):142-146.

Zheng J, He H, Kuang W, Yuan W. Presurgical nasoalveolar molding with 3D printing for a patient with unilateral cleft lip, alveolus, and palate. *Am J Orthod Dentofacial Orthop*. 2019;156(3):412-419.

Zheng Y, Lu B, Zhang J, Wu G. CAD/CAM silicone simulator for teaching cheiloplasty: description of the technique. *Br J Oral Maxillofac Surg*. 2015;53(2):194-196.

Zheng Y, Zhang D, Qin T, Wu G. Correction of nasal deformity in infants with unilateral cleft lip and palate using multiple digital techniques. *J Prosthet Dent*. 2016;115(6):788-791.