symmetry

MDPI

Article

3D Printed Personalized Corneal Models as a Tool for Improving Patient's Knowledge of an Asymmetric Disease

Jose S. Velázquez [1], Francisco Cavas [1,*], José M. Bolarín [2] and Jorge L. Alió [3,4,5]

1 Department of Structures, Construction and Graphical Expression, Technical University of Cartagena, 30202 Cartagena, Spain; jose.velazquez@upct.es
2 Technology Centre for IT and Communications (CENTIC), Scientific Park of Murcia, 30100 Murcia, Spain; bolarin5@hotmail.com
3 Division of Ophthalmology, Miguel Hernández University, 03550 Alicante, Spain; jlalio@vissum.com
4 Keratoconus Unit of Vissum Corporation, 03016 Alicante, Spain
5 Department of Refractive Surgery, Vissum Corporation, 03016 Alicante, Spain
* Correspondence: francisco.cavas@upct.es; Tel.: +34-968-328856

Received: 19 December 2019; Accepted: 9 January 2020; Published: 11 January 2020

Abstract: Additive manufacturing is a vanguard technology that is currently being used in several fields in medicine. This study aims to evaluate the viability in clinical practice of a patient-specific 3D model that helps to improve the strategies of the doctor-patient assistance. Data obtained from a corneal topographer were used to make a virtual 3D model by using CAD software, to later print this model by FDM and get an exact replica of each patient's cornea in consultation. Used CAD and printing software were open-source, and the printing material was biodegradable and its cost was low. Clinic users gave their feedback by means of a survey about their feelings when perceiving with their senses their own printed cornea. There was 82 surveyed, 73.8% (9.74; SD: 0.45) of them considered that the model had helped them a lot to understand their disease, expressing 100% of them their intention of taking home the printed model. The majority highlighted that this new concept improves both quality and clinical service in consultation. Custom-made individualized printed models allow a new patient-oriented perspective that may improve the communication strategy from the ophthalmologist to the patient, easing patient's understanding of their asymmetric disease and its later treatment.

Keywords: computer-aided geometric design (CAGD); additive manufacturing (AM); scheimpflug; low cost

1. Introduction

Keratoconus (KC) is an asymmetric condition in which the cornea, at a local level, becomes thinner and develops a cone-like bulge. Prevalence of this corneal degeneration is variable: many studies suggest a value ranging from 50 to 230 cases per 10,000, due to variability of diagnostic criteria. Keratometry, slit-lamp biomicroscopy, corneal topography and retinoscopy are the most common exams used for KC diagnosis [1,2].

Currently, there is an increasing need from patients to be better informed about clinical practice [3], however, improving patient information in ophthalmology consultations remains a clinical challenge [4], as ophthalmologists develop their doctor-patient assistance strategies using conventional techniques based in bi-dimensional (2D) images [5]. Many of the patients that attend consultations suffer from severely diminished visual acuity, something that is particularly frequent in advanced cases of KC, impeding the explanation of their pathology to them by means of drawn pictures or 3D renders on

a screen. Consequently, as patients cannot take advantage from the benefits of three-dimensional (3D) images to spatially conceptualize the real extent of their pathology, new approaches need to be explored in the patient–doctor's communication process.

The fundamental pillar for a successful clinical consultation is the ability that the ophthalmologist shows to manage patient expectations, as frequently patients do not understand the true nature of their medical condition in KC disease, which leads to a scenario of frustration and poor outcomes [6]. In clinical practice, several authors have demonstrated that the use of physical 3D models of biological structures improves the understanding of the disease by the patients [7–9], which suggests that the use of senses over a three-dimensional physical model makes patient's learning easier, providing a better understanding of the pathology and its later treatment. Thus, it would be of great interest, in the field of ophthalmology, to develop a new concept of information and education of patients that promoted success in ophthalmological consultations (Figure 1).

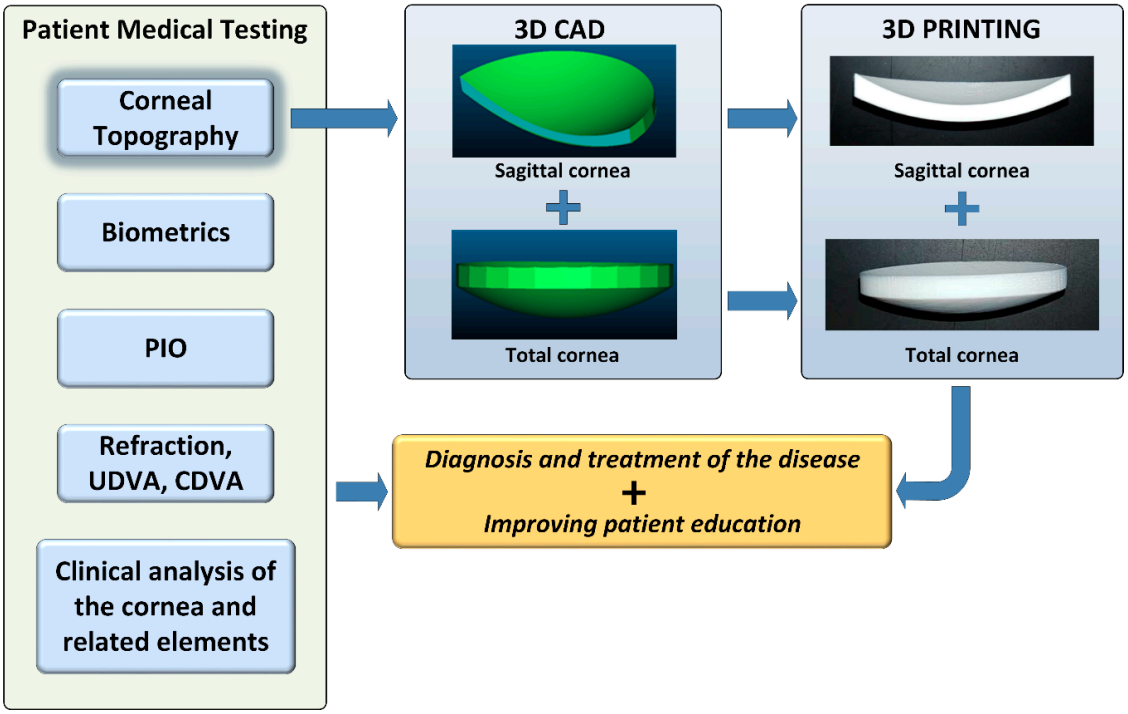

Figure 1. New concept of information and education in clinical practice.

Additive manufacturing (AM) is a disruptive and sustainable innovation [10] that allows the fabrication of three-dimensional (3D) objects. This term comprises many subcategories, such as rapid prototyping, direct digital manufacturing (DDM) and 3D printing (3DP), among others [11], all of them increasingly useful in automotive [12,13] and aerospace/defense [14,15] industries. When combined with reverse engineering and CAD modeling techniques, AM technologies can end up the design process in engineering, allowing more freedom when designing, higher customization, less waste production and manufacturing complex structures in a faster way [16,17].

In the field of medicine, AM technology is used for the manufacture of highly customized vanguard devices, as well as printing tissues and soft organs [6]. In addition, the advent of new technologies has propelled AM to become an accessible and cost-effective technology for medical community [18], being it also used in different fields for the fabrication of personalized models used in surgical planning, residents teaching or patients education [19–29]. Furthermore, these designs are frequently available in the Internet in open access for the medical community, promoting the development of collaborative networks between doctors and researchers, which turns them into a fundamental tool in translational research [30,31].

Our research group has validated a virtual 3D model of the cornea for each specific patient by using proprietary software [32]. These models have been used for the diagnosis of KC in virtual environments [33,34], but can also be used for 3D printing, so the printed physical model will reflect the abnormal irregularities and asymmetry that characterizes the cornea as KC disease progresses, in a way that patients would be capable of conceiving the geometrical variability of their cornea comparing it with a healthy one. This way, patients will be able to conceptualize the physical cause that inducts their loss of visual acuity, and consequently, their quality of life. Furthermore, and in the framework of promotion of the collaborative research networks, in this research work we propose the use of open-source software for the generation of the files of the virtual 3D models of the patients, so they can be used for any member of the international scientific community.

Thus, in this research work, it is proposed a new concept of patient information that uses 3D printed models of the cornea in the clinical practice of a hospital, using for its creation open-source software, both for the generation of the CAD models and the 3D printing files. The main objective pursued is improving the communication strategy of the ophthalmologist with the patient, easing the patient's process of understanding their disease and its later treatment, and avoiding a situation in which patients do not realize the real dimension of their disease, that could lead them to a scenario of frustration and poor outcomes.

2. Material and Methods

2.1. Patients

This article presents an observational comparative study that included 30 corneas of healthy patients (13 men and 17 women, average age 28.01 ± 14.19) and 52 of patients with keratoconus (22 men and 30 women, average age 26.71 ± 13.41). Keratoconus patients were also divided in several sub-groups, depending on the disease severity in the Amsler-Krumeich grading system [2,35]: 20 grade I, 14 grade II, 12 grade III and 6 grade IV.

The tenets of the Declaration of Helsinki (7th rev., Oct-2013, Fortaleza, Brazil) were followed for the development of the research, and it was backed up by the Committee of Ethics of the hospital participating in this study, signing all patients their consent to participate. The subjects whose data were used in this study were diagnosed in Vissum Corporation Alicante (a centre in affiliation with Miguel Hernández University of Elche, Spain), and their data is stored in the "Iberia" database of KC eyes that has been developed for the National Network for Clinical Research In Ophthalmology RETICS-OFATARED.

The procedure to discriminate between normal and KC patients was made according to validated up-to-date topographical and clinical verifications [2,5]. The exclusion criteria were the subsequent: contact lenses use in the thirty days that preceded their initial visit, ocular surface irritation, any previous ocular surgical procedure, mild or acute dry eye or presence of any other ocular comorbidity. Healthy eyes selected were all those that did not coincide with any of the exclusion criteria, while the diagnosis of keratoconus according to standard guidelines was the criterion to be included in the KC group.

2.2. Methods

Corneal tomographers based on Scheimpflug technology allow us to obtain a file in comma-separated values (CSV format), which can be used for different studies [36–39]. This file is composed of a spatial cloud of points in matrix form that represent corneal surfaces [32].

In this research work, Sirius tomographer (CSO, Italy) has been used. It is equipment that has proved its validity in clinical practice [5]. For the selection of data, just the topographies showing the highest acquisition quality were included in the study.

The custom-made individualized printed model reconstruction procedure consists of the following successive stages (Figure 2): I) surface and 3D model generation, II) 3D printable model preparation and III) 3D model printing in clinical practice.

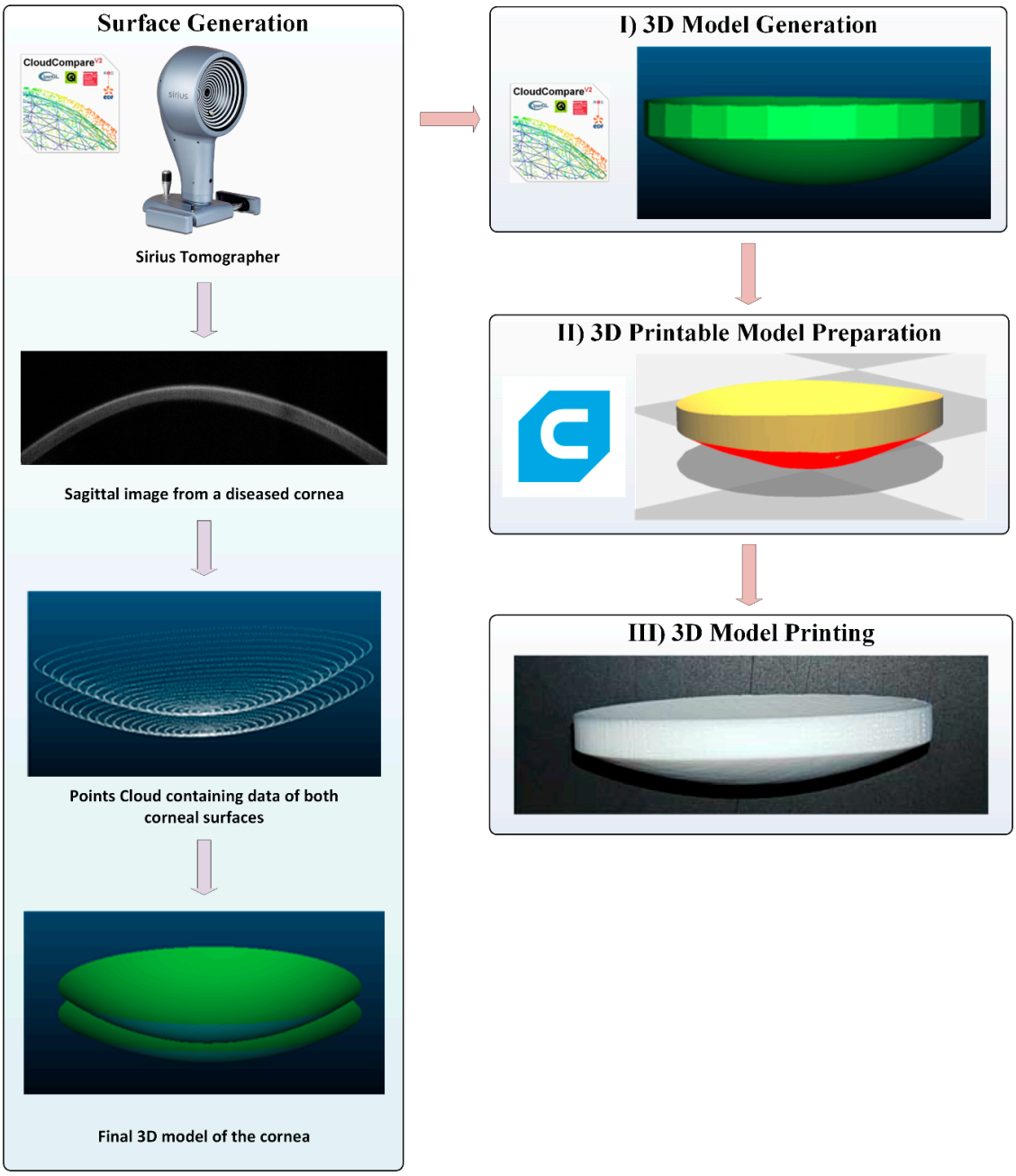

Figure 2. Proposed methodology for custom-made individualized model printing.

I. Surface and 3D model generation. At this point, a volumetric dataset was calculated from the available CSV file. This task can be performed by several software applications. In this study, CloudCompare 2.9.1 open-source software was the one used to generate the 3D model, using its "Delaunay 2.5D (best fitting plane)" option to generate a mesh from the point cloud of each surface. Then, the perimeter surface was created and, using Boolean operations, it was merged with the anterior and posterior corneal surfaces to create the final volume, which was then cut by a sagittal plane that passed through the optical axis and the minimum thickness points (anterior/posterior) of the corneal surfaces. CloudCompare entities are saved as BIN files, a format that is highly compatible with most open source 3D graphics software, so they can be easily used by any collaborative research network.

II. 3D Printable Model Preparation. 3D Printing process needs to define the surfaces of the solid model as a polygonal triangle mesh. However, even doing so, the virtual 3D model is still unfinished and its rough borders have to be refined. Other surface improvements can also be done, such as

inspecting and modifying any overlying surfaces, and simplifying the image file to increase printing efficiency. For this purpose, Cura 2.5 free software (Ultimaker, Netherlands) was used. To do so, files generated in CloudCompare were exported into STL (Stereolithography, Standard Triangle Language or Standard Tessellation Language) format [40], which is a very versatile and greatly compatible format with all 3D printers. Then, printing parameters were set in Cura, and a file containing all printing information (points, trajectories, speed, filling, etc.) was then generated as a GCODE file, which was lately uploaded to the 3D printer controller using a USB pendrive. 3D model files (.stl) and printing information files (.gcode) for both a healthy and an advanced KC cornea, complete and by a sagittal cut, have been attached as Supplementary Materials.

III. 3D Printing. The printer selected for this project was a FDM (fused deposition modeling) model designed by the UPCT-Makers organization, named "3D Printer ETSII –UPCT" [41]. This 3D printer is part of the RepRap project [42], so its drawings and technical data are open-source and available in the Internet, allowing its construction by any user. It was endowed with an Arduino MEGA controller, RAMPS 1.4 and drivers V. 88.25, and was programmed with Marlin software. It can be considered a low cost printer, as it had an approximate cost of less than 120 €, with an average life expectancy of 2000 duty hours.

The material used for 3D printing was polylactic acid (PLA), it is a rigid biodegradable polymer [43], that is stable to ultra-violet light, has low flammability and its characteristics are similar to PET polymer. Its properties, along with main printing parameters, can be checked in Table 1.

Table 1. 3D printer parameters.

Parameter	Values/Settings
Material	PLA
Quality: layer height	0.2–0.3 mm
Fusing material density	1.25 g/cm^3
Fusing material fusion point	160 °C
Printing temperature	225 °C
Nozzle diameter	1 mm
Flow rate	100%
Print speed	500 mm/s
Travel speed	130 mm/s
Printing area	22 cm × 23 cm × 20 cm

In our study, two physical models of cornea were printed per patient: a complete cornea, which corresponds to its full structure geometry, in which patient can see and perceive with his own senses the possible existence of morphological alterations at surface (anterior/posterior) level and the corneal volume; and another cornea, which corresponds to one half of a full cornea, defined by a sagittal plane that passes through the geometrical axis and the minimum thickness points (anterior/posterior) of the corneal surfaces (Figure 3), in which the patient can perceive with his senses the possible existence of morphological alterations in corneal thickness and the variation of curvature at surface (anterior/posterior) level.

As corneal real diameter is about 12 mm, and at that size corneal alterations were difficult to perceive, the use of a 1:1 scale for the model was discarded. Conversely, using big size models makes perception easier, but also significantly increases printing costs, so finally a 5:1 scale was used, as it was the smallest one that allowed an easy detection of slight changes in thickness and/or curvature.

The average time for all the process (3D modeling and 3D printing) was of 24.8 ± 3.4 min.

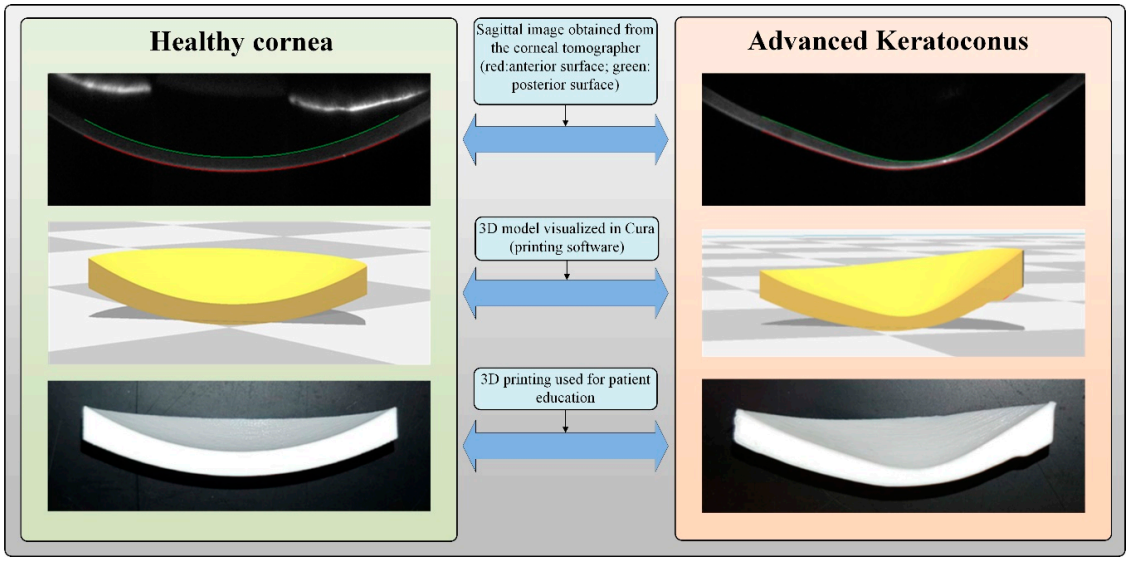

Figure 3. Healthy cornea (male patient of 24 years, Oculus Sinister (OS), Corrected Distance Visual Acuity (CDVA) = 1, astigmatism = 0.45, comma of like = 0.27, spherical-like = 0.23, Q8mm = −0.16 central thickness= 534). Advanced keratoconus (female patient of 20 years, Oculus Dexter (OD), CDVA = 0.44, astigmatism = 1.17, comma of like = 2.27, spherical-like = 2.50, Q8mm = −2.42 central thickness = 402).

2.3. Questionnaire

Finally, in order to assess the usefulness of the 3D model, a questionnaire was passed to each patient (82 in total). If the patient suffered from keratoconus, his custom 3D printed model was compared with a typical healthy cornea model, and their condition was explained to them, filling the questionnaire just after finishing the explanation. Questions made can be seen in Table 2. When selecting the scale for each question, for Q1, Q2 and Q5 we used 10 levels Likert items instead of the most common five level ones, looking for minimizing central tendency bias, while for questions Q3 and Q4, we opted for an absolute scale (yes/no/neutral).

Table 2. Questions made to the patients.

Number	Question Test	Possible Answer
Q1	What usefulness do you attribute to this custom 3D model?	From 1 = not useful at all to 10 = very useful
Q2	How much did the custom 3D model help you to better understand your condition?	From 1 = nothing at all to 10 = a huge lot
Q3	Would you like to take the custom 3D model with you after the consultation?	Yes/No/Neutral
Q4	Would you consider that using this custom 3D model improves the quality of our clinical service?	Yes/No/Neutral
Q5	How much do you consider that patients would benefit from the use of these custom 3D models in consultations?	From 1 = nothing at all to 10 = a huge lot

3. Results

The study lasted from January 2018 to March 2019, in Vissum Hospital in Alicante (Spain). Table 3 reports the collected answers to the five questions proposed to the patients.

Table 3. Questionnaire results.

Number	Possible Answer	Percentage	Average	Standard Deviation (SD)
Q1	From 1 = not useful at all to 10 = very useful	-	9.67	0.53
Q2	From 1 = nothing at all to 10 = a huge lot	-	9.74	0.45
Q3	Yes No Neutral	100.0 0.0 0.0		
Q4	Yes No Neutral	95.2 0.0 4.8		
Q5	From 1 = nothing at all to 10 = a huge lot	-	8.62	0.58

Results of Q1 show that the majority of patients found the 3D custom model "very useful", with more than half of the answers (69%) placed in top of the graduated scale (9.67; SD:0.53).

Similarly, 73.8% of patients considered that the use of the 3D personalized model had helped them "a huge lot" to understand their disease (9.74; SD: 0.45) when they answered question Q2.

In relation with question Q3, 100% of patients expressed their will to take the model home with them.

Results of question Q4 show that the vast majority of (95.2%) consider that the use of the personalized 3D model improves the clinical service rendered, being remarkable that only 4.8% believe that it does not make it better nor worse, and none of them consider that it makes it worse.

Finally, the results of question Q5 suggest that patients have considered that the use of personalized 3D models has improved the clinical service rendered in a high degree (8.62; SD:0.58).

To estimate the cost of realization of the 3D model, we considered the following: cost of data acquisition (0 €, included in consultation costs), proportional part of the cost of buying of the printer (120 € divided by 2000 h of life, 0.06 € per hour), labor of the laboratory technician (6 min at 5.66 €/hour, 0.57 €), software (0 €, as it was all open source) and material (30 g. of PLA at 18 €/kg, 0.47 €). The final estimated cost for each piece was around 1.10 €.

4. Discussion

In medical consultation, it has been demonstrated that a combination of both physical models and conventional 2D techniques of bone structures, gives patients a better comprehension of their disease [44]. Furthermore, in terms of teaching human anatomy, it has been proved that physical 3D models are more efficient to determine the existence of the disease than corpse models [45,46].

Physical 3D modeling has the capability of creating exact models of the human anatomy, thus being a fundamental tool not only for research [47], but also to educate patients [3].

However, using AM for biomedical applications has also its limitations: small anatomical features and structural details are difficult to replicate, and the number of biocompatible materials and resins available is limited, making AM expensive sometimes [48].

In the field of ophthalmology, AM applications are, conceptually speaking, not very different from the ones used in other fields of medicine. In scientific literature, there have been described works related with the printing of the first artificial cornea [49], fetal face modeling [50], intraocular lenses [51–54] or rigid permeable gas contact lenses [55], ocular prosthesis [56–59], intraocular tumor visualization [60], medical staff education [61,62], tissue bio-printing [63–65], printing of surgical instruments [66] or medical devices [67] or goggles for patients with deformations of unusual facial features [68]. However, we have not found proof of the use of the AM as a tool for improving doctor–patient communication strategies in KC disease.

In this research work, we describe our experience using AM techniques in ophthalmological clinical practice to obtain a custom-made individualized printed model, by means of a low-cost material, such as PLA. The objective is that patients acquire, basing on the physical model built, knowledge of the real dimension of the asymmetrical morphological changes that their cornea suffers when the disease progresses, and that affect their optical capacity, and therefore their quality of life.

For the building of the physical model, it is necessary to start from a virtual 3D model. However, in all different collaborative platforms of medical research related with virtual models [30,31,69], we have not found any virtual models of healthy or keratoconus-diagnosed corneas. Thus, virtual models have been generated from the data provided by the Sirius (CSO, Italy) tomographer, by using the open-source software CloudCompare, although these data can be obtained from any tomographer based in Scheimpflug technology [5]. In our study, two virtual models have been generated for each patient, one of a complete cornea, and another of a cornea with a sagittal cut defined from the minimum thickness points. These virtual models can be a fundamental tool in translational research, if shared through the collaborative open-access platforms [69].

From these patient-specific virtual models, and using open-source software, as well as low-cost and freely available manufacture hardware, the physical models used in this study were produced.

For this work, different printing speeds, layer thicknesses and nozzle sizes were tested, and it could be observed that a higher speed generally implied higher layer thicknesses, and therefore, a worse surface finishing in the model, which is in accordance with other authors works [70]. Finally, we opted for the speed, thickness and nozzle size indicated in Table 1 to get an acceptable surface finishing, with printing times below 30 min, that is the mean time that patients wait after the clinical tests to enter the doctor's consultation to be informed of the diagnosis. With these parameters, the printing is a bit cheaper than usual in other cases [71], and gives printed cornea a "stepped" aspect, although with enough precision to show, in an evident way, the differences between a normal cornea and one with its thickness locally diminished.

The fabrication cost of the 3D printed model, due to its simplicity and low cost of PLA, was of only 1.10 € each, which remains wide below the 490 € that can cost a model of more complex organs, such as kidneys, made in photopolymer materials [72].

Regarding the questionnaire answers, results of Q1 confirm the results obtained in other similar studies [73]. Similarly, answers to question Q2 are in line with what have been observed in other previous investigations, which used 3D models to explain patients their condition or the surgery that they will undergo [72]. Furthermore, the results obtained are in line with the ones obtained by Precee et al. [7], who demonstrated that the use of the touch and sight senses, with regard to a physical 3D model, improve the learning curve of the patients in relation with their disease.

In relation with question Q3, results contrast with the results obtained in other studies, in which 39% of the patients expressed that they would not be interested in buying the model [71], and can be explained by the fact that the low fabrication cost of the model allows the clinic to offer this service without any additional charge to the patient, integrating its cost in the cost of the medical consultation itself, making the patient more willing to take it home.

Results of question Q4 are in line with the ones presented by other authors, in which they demonstrated the usefulness of the 3D printing to improve the education in clinical practice [18], more precisely, in this study 95.8% of the surveyed considered useful the 3D models.

Finally, the results of question Q5 are in line with the values obtained for other studies (9.4/10) when patients have been asked about the degree of satisfaction with the medical services after the use of 3D models for their education [72].

Our study has, however, some limitations. First, the cross-sectional nature of the study presents a limited extension of the patient's cohort due to the low prevalence of this corneal degeneration; and second, the use of patients of just one hospital for the study. A longitudinal study with a larger sample size and including patients from different hospitals would be needed to further investigate the clinical

utility and viability, in clinical practice, of a patient-specific 3D model that helped to improve the strategies in doctor–patient assistance.

5. Conclusions

In this paper, the authors evaluated the possible benefits of using custom made 3D printed models of the cornea as a tool for increasing patient's knowledge and understanding of their asymmetric condition, with the aim of improving the level of quality perceived for the services rendered in medical consultations.

The results show that owning a custom 3D printed model of their cornea was considered interesting for the totality of the patients that participated in the study, and that the comparison of their pathologic cornea with the 3D model of a healthy one, helped them "a lot" (9.71/10, SD:0.45) to understand their disease, considering the vast majority (>95%) of the participants that using the 3D printed realistic models increased the quality of services rendered in the clinic.

In addition, the use of open-source and free software, as well as a RepRap 3D printer, whose drawings are available for everyone, make the approach described in this work accessible not only to high-end clinics, but to any clinic, whatever its budget is.

In conclusion, 3D printing has allowed the creation of precise physical models that reflects asymmetric modifications due to keratoconus pathology. The visual and tactile perception of these models allow patients to better understand and manage the perspective of treatment of their disease, making the clinicians job more efficient and therefore increasing the perception of quality of the service they render.

Although the use of 3D printing is increasing currently, the true potential of this technology will be achieved when function and form become fully integrated, as for example happens in the bio printing of tissues or organs, such as the cornea, that even if it has not been fully reached yet, the first steps have started to be successfully taken [49].

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-8994/12/1/151/s1.

Author Contributions: Conceptualization, J.S.V. and F.C.; methodology, J.S.V., F.C. and J.L.A.; validation, J.S.V. and J.M.B.; analysis, F.C. and J.M.B.; investigation, J.S.V., F.C. and J.L.A.; resources, J.S.V. and F.C.; data curation, J.M.B. and J.L.A.; writing—original draft preparation, J.S.V. and F.C.; writing—review and editing F.C., J.M.B. and J.L.A.; supervision, J.L.A.; project administration, F.C. and J.L.A.; funding acquisition J.L.A. All authors have read and agreed to the published version of the manuscript.

Funding: This publication has been carried out in the framework of the Thematic Network for Co-Operative Research in Health (RETICS), reference number RD16/0008/0012, financed by the Carlos III Health Institute–General Subdirection of Networks and Cooperative Investigation Centers (R&D&I National Plan 2013–2016) and the European Regional Development Fund (FEDER).

Acknowledgments: The authors wish to thank all subjects participating in this study.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Rabinowitz, Y.S. Keratoconus. *Surv. Ophthalmol.* **1998**, *42*, 297–319. [CrossRef]
2. Cavas-Martinez, F.; De la Cruz Sanchez, E.; Nieto Martinez, J.; Fernandez Canavate, F.J.; Fernandez-Pacheco, D.G. Corneal topography in keratoconus: State of the art. *Eye Vis. (Lond. UK)* **2016**, *3*, 5. [CrossRef] [PubMed]
3. Salisbury, H. Helen Salisbury: The informed patient. *BMJ* **2019**, *364*, l638. [CrossRef] [PubMed]
4. Huang, W.; Zhang, X. 3D Printing: Print the future of ophthalmology. *Investig. Ophthalmol. Vis. Sci.* **2014**, *55*, 5380–5381. [CrossRef]
5. Pinero, D.P. Technologies for anatomical and geometric characterization of the corneal structure and anterior segment: A review. *Semin. Ophthalmol.* **2015**, *30*, 161–170. [CrossRef]
6. Bauermeister, A.J.; Zuriarrain, A.; Newman, M.I. Three-Dimensional Printing in Plastic and Reconstructive Surgery: A Systematic Review. *Ann. Plast. Surg.* **2016**, *77*, 569–576. [CrossRef]
7. Preece, D.; Williams, S.B.; Lam, R.; Weller, R. "Let's get physical": Advantages of a physical model over 3D computer models and textbooks in learning imaging anatomy. *Anat. Sci. Educ.* **2013**, *6*, 216–224. [CrossRef]

8. Watson, R.A. A low-cost surgical application of additive fabrication. *J. Surg. Educ.* **2014**, *71*, 14–17. [CrossRef]
9. Hoang, D.; Perrault, D.; Stevanovic, M.; Ghiassi, A. Surgical applications of three-dimensional printing: A review of the current literature & how to get started. *Ann. Transl. Med.* **2016**, *4*, 456. [CrossRef]
10. Labonnote, N.; Rønnquist, A.; Manum, B.; Rüther, P. Additive construction: State-of-the-art, challenges and opportunities. *Autom. Constr.* **2016**, *72*, 347–366. [CrossRef]
11. Gibson, I.; Rosen, D.; Stucker, B. *Additive Manufacturing Technologies: 3D Printing, Rapid Prototyping, and Direct Digital Manufacturing*, 2nd ed.; Springer: New York, NY, USA, 2015; pp. 1–498. [CrossRef]
12. Böckin, D.; Tillman, A.M. Environmental assessment of additive manufacturing in the automotive industry. *J. Clean. Prod.* **2019**, *226*, 977–987. [CrossRef]
13. Goh, G.D.; Dikshit, V.; Nagalingam, A.P.; Goh, G.L.; Agarwala, S.; Sing, S.L.; Wei, J.; Yeong, W.Y. Characterization of mechanical properties and fracture mode of additively manufactured carbon fiber and glass fiber reinforced thermoplastics. *Mater. Des.* **2018**, *137*, 79–89. [CrossRef]
14. Espalin, D.; Muse, D.W.; MacDonald, E.; Wicker, R.B. 3D Printing multifunctionality: Structures with electronics. *Int. J. Adv. Manuf. Technol.* **2014**, *72*, 963–978. [CrossRef]
15. Mangum, P., Jr.; Fisher, Z.; Cooksey, K.D.; Mavris, D.; Spero, E.; Gerdes, J.W. An automated approach to the design of small aerial systems using rapid manufacturing. In Proceedings of the ASME 2015 International Design Engineering Technical Conferences and Computers and Information in Engineering Conference, Boston, MA, USA, 2–5 August 2015.
16. Ngo, T.D.; Kashani, A.; Imbalzano, G.; Nguyen, K.T.Q.; Hui, D. Additive manufacturing (3D printing): A review of materials, methods, applications and challenges. *Compos. B Eng.* **2018**, *143*, 172–196. [CrossRef]
17. Tucker, C.S.; Saint John, D.B.; Behoora, I.; Marcireau, A. Open source 3D scanning and printing for design capture and realization. In Proceedings of the ASME 2014 International Design Engineering Technical Conferences and Computers and Information in Engineering Conference, Buffalo, NY, USA, 17–20 August 2014.
18. Jones, D.B.; Sung, R.; Weinberg, C.; Korelitz, T.; Andrews, R. Three-Dimensional Modeling May Improve Surgical Education and Clinical Practice. *Surg. Innov.* **2016**, *23*, 189–195. [CrossRef]
19. Abudayyeh, I.; Gordon, B.; Ansari, M.M.; Jutzy, K.; Stoletniy, L.; Hilliard, A. A practical guide to cardiovascular 3D printing in clinical practice: Overview and examples. *J. Interv. Cardiol.* **2018**, *31*, 375–383. [CrossRef]
20. Jastifer, J.R.; Gustafson, P.A. Three-Dimensional Printing and Surgical Simulation for Preoperative Planning of Deformity Correction in Foot and Ankle Surgery. *J. Foot Ankle Surg. Off. Publ. Am. Coll. Foot Ankle Surg.* **2017**, *56*, 191–195. [CrossRef]
21. Pucci, J.U.; Christophe, B.R.; Sisti, J.A.; Connolly, E.S., Jr. Three-dimensional printing: Technologies, applications, and limitations in neurosurgery. *Biotechnol. Adv.* **2017**, *35*, 521–529. [CrossRef]
22. Soon, D.S.; Chae, M.P.; Pilgrim, C.H.; Rozen, W.M.; Spychal, R.T.; Hunter-Smith, D.J. 3D haptic modelling for preoperative planning of hepatic resection: A systematic review. *Ann. Med. Surg.* **2016**, *10*, 1–7. [CrossRef]
23. Zhong, N.; Zhao, X. 3D printing for clinical application in otorhinolaryngology. *Eur. Arch. Otorhinolaryngol.* **2017**, *274*, 4079–4089. [CrossRef]
24. Tanner, J.A.; Jethwa, B.; Jackson, J.; Bartanuszova, M.; King, T.S.; Bhattacharya, A.; Sharma, R. A Three-Dimensional Print Model of the Pterygopalatine Fossa Significantly Enhances the Learning Experience. *Anat. Sci. Educ.* **2020**. [CrossRef] [PubMed]
25. Barabas, J.I.; Ghimessy, A.K.; Renyi-Vamos, F.; Kocsis, A.; Agocs, L.; Meszaros, L.; Pukacsik, D.; Andi, J.; Laki, A.; Voros, F.; et al. Innovation in medicine: Opportunities of 3D modeling and printing for perioperative care of cardio and thoracic surgical patients. Experiences in Hungary. *Orv. Hetil.* **2019**, *160*, 1967–1975. [CrossRef] [PubMed]
26. Panesar, S.S.; Magnetta, M.; Mukherjee, D.; Abhinav, K.; Branstetter, B.F.; Gardner, P.A.; Iv, M.; Fernandez-Miranda, J.C. Patient-specific 3-dimensionally printed models for neurosurgical planning and education. *Neurosurg. Focus* **2019**, *47*, E12. [CrossRef] [PubMed]
27. Kim, P.S.; Choi, C.H.; Han, I.H.; Lee, J.H.; Choi, H.J.; Lee, J.I. Obtaining Informed Consent Using Patient Specific 3D Printing Cerebral Aneurysm Model. *J. Korean Neurosurg. Soc.* **2019**, *62*, 398–404. [CrossRef] [PubMed]
28. Biro, M.; Kim, I.; Huynh, A.; Fu, P.; Mann, M.; Popkin, D.L. The use of 3-dimensionally printed models to optimize patient education and alleviate perioperative anxiety in Mohs micrographic surgery: A randomized controlled trial. *J. Am. Acad. Dermatol.* **2019**, *81*, 1339–1345. [CrossRef]
29. Zhuang, Y.D.; Zhou, M.C.; Liu, S.C.; Wu, J.F.; Wang, R.; Chen, C.M. Effectiveness of personalized 3D printed models for patient education in degenerative lumbar disease. *Patient Educ. Couns.* **2019**, *102*, 1875–1881. [CrossRef]

30. Gross, B.C.; Erkal, J.L.; Lockwood, S.Y.; Chen, C.; Spence, D.M. Evaluation of 3D printing and its potential impact on biotechnology and the chemical sciences. *Anal. Chem.* **2014**, *86*, 3240–3253. [CrossRef]
31. National Institutes of Health. 3D Print Exchange. Available online: http://3dprint.nih.gov (accessed on 13 May 2019).
32. Cavas-Martinez, F.; Fernandez-Pacheco, D.G.; de la Cruz-Sanchez, E.; Nieto Martinez, J.; Canavate, F.J.F.; Alio, J.L. Virtual biomodelling of a biological structure: The human cornea. *Dyna* **2015**, *90*, 647–651.
33. Cavas-Martinez, F.; Bataille, L.; Fernandez-Pacheco, D.G.; Canavate, F.J.F.; Alio, J.L. Keratoconus Detection Based on a New Corneal Volumetric Analysis. *Sci. Rep.* **2017**, *7*, 15837. [CrossRef]
34. Cavas-Martinez, F.; Bataille, L.; Fernandez-Pacheco, D.G.; Canavate, F.J.F.; Alio, J.L. A new approach to keratoconus detection based on corneal morphogeometric analysis. *PLoS ONE* **2017**, *12*, e0184569. [CrossRef]
35. Krumeich, J.H.; Daniel, J.; Knulle, A. Live-epikeratophakia for keratoconus. *J. Cataract. Refract. Surg.* **1998**, *24*, 456–463. [CrossRef]
36. Ariza-Gracia, M.A.; Zurita, J.; Pinero, D.P.; Calvo, B.; Rodriguez-Matas, J.F. Automatized Patient-Specific Methodology for Numerical Determination of Biomechanical Corneal Response. *Ann. Biomed. Eng.* **2016**, *44*, 1753–1772. [CrossRef] [PubMed]
37. Asher, R.; Gefen, A.; Moisseiev, E.; Varssano, D. An analytical approach to corneal mechanics for determining practical, clinically-meaningful patient-specific tissue mechanical properties in the rehabilitation of vision. *Ann. Biomed. Eng.* **2015**, *43*, 274–286. [CrossRef] [PubMed]
38. Lanchares, E.; Del Buey, M.A.; Cristobal, J.A.; Calvo, B. Computational Simulation of Scleral Buckling Surgery for Rhegmatogenous Retinal Detachment: On the Effect of the Band Size on the Myopization. *J. Ophthalmol.* **2016**, *2016*, 3578617. [CrossRef] [PubMed]
39. Simonini, I.; Pandolfi, A. Customized Finite Element Modelling of the Human Cornea. *PLoS ONE* **2015**, *10*, e0130426. [CrossRef] [PubMed]
40. Grimm, T. *User's Guide to Rapid Prototyping*; Society of Manufacturing Engineers: Dearborn, MI, USA, 2004.
41. ETSII UPCT Printer/es. Available online: https://reprap.org/mediawiki/index.php?title=ETSII_UPCT_Printer/es&oldid=156702 (accessed on 3 June 2019).
42. Jones, R.; Haufe, P.; Sells, E.; Iravani, P.; Olliver, V.; Palmer, C.; Bowyer, A. RepRap—The replicating rapid prototyper. *Robotica* **2011**, *29*, 177–191. [CrossRef]
43. Sanchez-Tena, M.A.; Alvarez-Peregrina, C. Application of 3D Printing Technology in Scleral Cover Shell Prosthesis. *J. Med. Syst.* **2019**, *43*, 149. [CrossRef]
44. Hughes, A.J.; DeBuitleir, C.; Soden, P.; O'Donnchadha, B.; Tansey, A.; Abdulkarim, A.; McMahon, C.; Hurson, C.J. 3D Printing Aids Acetabular Reconstruction in Complex Revision Hip Arthroplasty. *Adv. Orthop.* **2017**, *2017*, 8925050. [CrossRef]
45. Banks, J. Adding value in additive manufacturing: Researchers in the United Kingdom and Europe look to 3D printing for customization. *IEEE Pulse* **2013**, *4*, 22–26. [CrossRef]
46. Ventola, C.L. Medical Applications for 3D Printing: Current and Projected Uses. *P T A Peer-Rev. J. Formul. Manag.* **2014**, *39*, 704–711.
47. Clemente, C.; Esposito, L.; Speranza, D.; Bonora, N. Firecracker eye exposure: Experimental study and simulation. *Biomech. Model. Mechanobiol.* **2017**, *16*, 1401–1411. [CrossRef] [PubMed]
48. Estomba, C.; González-Fernández, I.; Iglesias-Otero, M. 3D Printing for Biomedical Applications: Where are we now? *Eur. Med J.* **2017**, *2*, 16–22.
49. Isaacson, A.; Swioklo, S.; Connon, C.J. 3D bioprinting of a corneal stroma equivalent. *Exp. Eye Res.* **2018**, *173*, 188–193. [CrossRef] [PubMed]
50. Speranza, D.; Padula, F.; Motyl, B.; Tornincasa, S.; Marcolin, F.; Vezzetti, E.; Martorelli, M. Parenthood Perception Enhancement Through Interaction with 3D Printed Fetal Face Models. In *Advances on Mechanics, Design Engineering and Manufacturing II*; Springer: Cham, Switzerland, 2019; pp. 527–535.
51. Bassnett, S.; Shi, Y.; Vrensen, G.F. Biological glass: Structural determinants of eye lens transparency. *Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci.* **2011**, *366*, 1250–1264. [CrossRef]
52. Debellemaniere, G.; Flores, M.; Montard, M.; Delbosc, B.; Saleh, M. Three-dimensional Printing of Optical Lenses and Ophthalmic Surgery: Challenges and Perspectives. *J. Refract. Surg. (Thorofare NJ 1995)* **2016**, *32*, 201–204. [CrossRef]
53. Donaldson, P.J.; Grey, A.C.; Maceo Heilman, B.; Lim, J.C.; Vaghefi, E. The physiological optics of the lens. *Prog. Retinal Eye Res.* **2017**, *56*, e1–e24. [CrossRef]

54. Hejtmancik, J.F.; Shiels, A. Overview of the Lens. *Prog. Mol. Biol. Transl. Sci.* **2015**, *134*, 119–127. [CrossRef]
55. Zhao, F.; Zhao, G.; Weijie, F.; Chen, L. Application of 3D printing technology in RGPCL simulation fitting. *Med. Hypotheses* **2018**, *113*, 74–76. [CrossRef]
56. Callahan, A.B.; Campbell, A.A.; Petris, C.; Kazim, M. Low-Cost 3D Printing Orbital Implant Templates in Secondary Orbital Reconstructions. *Ophthalmic Plast. Reconstr. Surg.* **2017**, *33*, 376–380. [CrossRef]
57. Dave, T.V.; Tiple, S.; Vempati, S.; Palo, M.; Ali, M.J.; Kaliki, S.; Naik, M.N. Low-cost three-dimensional printed orbital template-assisted patient-specific implants for the correction of spherical orbital implant migration. *Indian J. Ophthalmol.* **2018**, *66*, 1600–1607. [CrossRef]
58. Fan, B.; Chen, H.; Sun, Y.J.; Wang, B.F.; Che, L.; Liu, S.Y.; Li, G.Y. Clinical effects of 3-D printing-assisted personalized reconstructive surgery for blowout orbital fractures. *Graefe's Arch. Clin. Exp. Ophthalmol.* **2017**, *255*, 2051–2057. [CrossRef] [PubMed]
59. Ruiters, S.; Sun, Y.; de Jong, S.; Politis, C.; Mombaerts, I. Computer-aided design and three-dimensional printing in the manufacturing of an ocular prosthesis. *Br. J. Ophthalmol.* **2016**, *100*, 879–881. [CrossRef] [PubMed]
60. Furdova, A.; Sramka, M.; Thurzo, A.; Furdova, A. Early experiences of planning stereotactic radiosurgery using 3D printed models of eyes with uveal melanomas. *Clin. Ophthalmol. (Auckl. N. Z.)* **2017**, *11*, 267–271. [CrossRef] [PubMed]
61. Adams, J.W.; Paxton, L.; Dawes, K.; Burlak, K.; Quayle, M.; McMenamin, P.G. 3D printed reproductions of orbital dissections: A novel mode of visualising anatomy for trainees in ophthalmology or optometry. *Br. J. Ophthalmol.* **2015**, *99*, 1162–1167. [CrossRef] [PubMed]
62. Scawn, R.L.; Foster, A.; Lee, B.W.; Kikkawa, D.O.; Korn, B.S. Customised 3D Printing: An Innovative Training Tool for the Next Generation of Orbital Surgeons. *Orbit (Amst. Neth.)* **2015**, *34*, 216–219. [CrossRef] [PubMed]
63. Kim, H.; Jang, J.; Park, J.; Lee, K.P.; Lee, S.; Lee, D.M.; Kim, K.H.; Kim, H.K.; Cho, D.W. Shear-induced alignment of collagen fibrils using 3D cell printing for corneal stroma tissue engineering. *Biofabrication* **2019**, *11*, 035017. [CrossRef]
64. Kim, H.; Park, M.N.; Kim, J.; Jang, J.; Kim, H.K.; Cho, D.W. Characterization of cornea-specific bioink: High transparency, improved in vivo safety. *J. Tissue Eng.* **2019**, *10*, 2041731418823382. [CrossRef]
65. Ludwig, P.E.; Huff, T.J.; Zuniga, J.M. The potential role of bioengineering and three-dimensional printing in curing global corneal blindness. *J. Tissue Eng.* **2018**, *9*, 2041731418769863. [CrossRef]
66. Navajas, E.V.; Ten Hove, M. Three-Dimensional Printing of a Transconjunctival Vitrectomy Trocar-Cannula System. *Ophthalmologica* **2017**, *237*, 119–122. [CrossRef]
67. Sommer, A.C.; Blumenthal, E.Z. Implementations of 3D printing in ophthalmology. *Graefe's Arch. Clin. Exp. Ophthalmol.* **2019**. [CrossRef]
68. Ayyildiz, O. Customised spectacles using 3-D printing technology. *Clin. Exp. Optom.* **2018**, *101*, 747–751. [CrossRef]
69. Kamali, P.; Dean, D.; Skoracki, R.; Koolen, P.G.L.; Paul, M.A.; Ibrahim, A.M.S.; Lin, S.J. The Current Role of Three-Dimensional (3D) Printing in Plastic Surgery. *Plast. Reconstr. Surg.* **2016**. [CrossRef] [PubMed]
70. Sukindar, N.A. Optimization of the Parameters for Surface Quality of the Open-source 3D Printing. *J. Mech. Eng.* **2017**, *SI3*, 33–43.
71. Speranza, D.; Citro, D.; Padula, F.; Motyl, B.; Marcolin, F.; Calí, M.; Martorelli, M. Additive Manufacturing Techniques for the Reconstruction of 3D Fetal Faces. *Appl. Bionics Biomech.* **2017**, *2017*, 9701762. [CrossRef] [PubMed]
72. Bernhard, J.C.; Isotani, S.; Matsugasumi, T.; Duddalwar, V.; Hung, A.J.; Suer, E.; Baco, E.; Satkunasivam, R.; Djaladat, H.; Metcalfe, C.; et al. Personalized 3D printed model of kidney and tumor anatomy: A useful tool for patient education. *World J. Urol.* **2016**, *34*, 337–345. [CrossRef] [PubMed]
73. Andolfi, C.; Plana, A.; Kania, P.; Banerjee, P.P.; Small, S. Usefulness of three-dimensional modeling in surgical planning, resident training, and patient education. *J. Laparoendosc. Adv. Surg. Tech.* **2017**, *27*, 512–515. [CrossRef] [PubMed]