ABSTRACT

Patients with Apert syndrome experience midfacial hypoplasia, hypertelorism, and downslanting palpebral fissures which can be corrected by midfacial bipartition distraction with rigid external distraction device (MBD-RED-frame). Quantitative studies typically focus on quantifying rigid advancement and rotation post-distraction, but intrinsic shape changes of bone and soft tissue remain unknown. This study presents a method to quantify these changes. Pre- and postoperative CT-scans from patients with Apert syndrome undergoing MBD-RED were collected. DICOM-files were converted to 3-dimensional bone and soft tissue reconstructions. Postoperative reconstructions were aligned on the preoperative maxilla, followed by non-rigid iterative closest point transformation to determine local shape changes. Anatomical point-to-point displacements were calculated and visualised using a heatmap and arrow map. Nine patients were included.

Zygomatic arches and frontal bone demonstrated the largest changes. Mid-lateral to supra-orbital rim showed an upward, inward motion. Mean bone displacements ranged from 3.3 – 12.8 millimetres. Soft tissue displacements were relatively smaller, with greatest changes at the lateral canthi. MBD-RED results in upward, inward rotation of the orbits, upward rotation of the zygomatic arch, and relative posterior motion of the frontal bone. Local movements were successfully quantified using a novel method, which can be applied to other surgical techniques/syndromes.

KEYWORDS

Apert Syndrome, Surgical outcomes, quantification, craniomaxillofacial surgery, rigid external distraction, soft tissue changes

INTRODUCTION

Children born with a craniofacial syndrome are affected by various facial deformities, such as midfacial hypoplasia, hyper/hypotelorism, as well as orbital and frontal bone malformations, and may require reconstructive surgery for both functional and aesthetic reasons. Facial reconstruction can be performed with or without the use of a rigid external distraction device (RED-frame).[1] Several RED-frame driven surgical techniques exist, and provide a gradual and rigid advancement of the facial skeleton as a whole or a selected craniomaxillofacial region. Monobloc distraction advances the frontal bone, orbits, and midface as one unit and Le Fort III advances the midface alone. Both procedures move large units of the facial skeleton without changing their intrinsic shape and work well in conditions such as Crouzon syndrome where the midface is retruded but the midfacial bone structure approximates to a normal shape.

Many craniofacial conditions such as Apert syndrome cause midfacial retrusion and also radically distort the intrinsic shape of the midfacial bones. Recognition of this fact has led to the development of osteotomies that change the shape of the midface and orbits. Midfacial bipartition distraction and Le Fort II with zygomatic osteotomies both represent attempts to treat the intrinsic flatness of the Apert midfacial skeleton and address other abnormalities such as hypertelorism and midfacial height disproportion.[2-5] These intrinsic changes in midfacial bone structure are difficult to quantify using conventional cephalometric and anthropometric measurements. Analysis of facial shape change is further complicated by the fact that the overlying soft tissues are abnormal and do not move in a one to one relationship with the underlying bones.

Adequate assessment of facial changes following craniofacial surgery is essential to improve the surgical technique, choice of procedure, and surgical planning. Several methodologies exist for the evaluation of the facial morphology and the movements due to distractive surgery; landmarked-based analysis has been applied to both two-dimensional (2D) and three-dimensional (3D) facial images. Traditional cephalometric analysis has been used to describe bone movements following various types of craniofacial surgeries, where the distances and angles were calculated from specific points on the 2D lateral view from the pre- and postoperative x-rays.[6, 7] The effects of midfacial bipartition distraction with RED-frame (MBD-RED), were analysed using pre- and post-operative computed tomography scans (CT-scans) by identifying anatomical landmarks on the 2D axial, sagittal and coronal planes of patients with Apert syndrome, a syndromic variation of craniosynostosis. This approach provided measurements of distances and angles in a 3D space for comparison of the pre- and postoperative states.[8] These methods rely on a few selected facial landmarks, however, a holistic analysis of the shape changes could not be performed.[9]

Automated methodologies that do not rely on facial landmarks have also been used to analyse the soft tissue and skeletal deformations.[10] This study made use of the rigid iterative closest point (ICP) registration algorithm to align the pre- and postoperative 3D reconstructions. The 3D shape displacements were then evaluated by determining the closest point-to-point correspondences between pre- and post-operative surface pairs, regardless of their anatomical correspondences. Closest points do not accurately represent the true displacements of different anatomical features.[11] To obtain the true anatomical point-to-point correspondences (i.e. anatomical correspondence, or dense correspondence), a more flexible version of rigid ICP, non-rigid ICP, can be applied to the 3D bone and soft tissue reconstructions. Non-rigid ICP uses a set of landmark points to guide the registration used to determine correspondences between the two 3D surfaces, and can therefore be used to obtain accurate anatomical correspondences, as opposed to closest-point-to-closest-point correspondence.[12] As a result, it can be used to determine the soft tissue shape deformations due to surgery using a set of 3D pre- and postoperative CT-scans.[10] For example, using non-rigid ICP, the preoperative coordinates of the tip of the nose, will also be identified as the tip of the nose, postoperatively. The identification of these anatomical points is essential for accurate pre- to postoperative assessment of shape changes. This methodology has not yet been applied to determine surgical outcomes on a skeletal level, which could allow not only the analysis of rigid movements (e.g., advancements and rotations due to the RED-frame distraction) using anatomical correspondence but also the smaller, more localised, 'intrinsic' changes as result of the distraction. Prior studies have analysed the rigid displacements and rotations that occur following RED-frame distraction, leaving the intrinsic, local bony changes due to distraction unknown. [6, 8, 13-15] While the soft tissue changes following these skeletal movements have been studied, the soft tissue response to the skeletal movement on a local level is unclear. Some studies have highlighted the challenges in determining how soft tissue displacements are driven by the skeletal movements, and non-linear relationships between bone and soft tissue displacements have been described. [14, 16, 17]

At *the Craniofacial Unit at Great Ormond Street Hospital for Children, London, UK* (GOSH), MBD-RED is the most commonly utilised mid facial osteotomy in Apert syndrome. It corrects hypertelorism, negative canthal axis, counterrotated orbits, and central midface hypoplasia. Prior studies, based on 2D landmark analysis or the rigid methodologies described above, showed that MBD-RED provides successful advancement of the central part of the face in patients with Apert syndrome and that the central part of the distracted region undergoes larger advancement than the lateral regions.[8, 13] These studies however did not provide any information about shape changes on a local level as a result of surgery.

This study presents a novel 3D morphometric analysis using a workflow methodology (pipeline). It quantifies the complex changes in hard and soft tissue topography and gives the surgeon insight into the changes induced by surgery.

MATERIAL AND METHODOLOGY

Dataset

Pre- and postoperative CT-scans of patients with Apert Syndrome who underwent MBD-RED at GOSH between 2005 and 2019 were collected. CT-scans of insufficient image quality, such as those with a limited number of slices or movement artefacts, were excluded, as were patients who did not have both pre- and postoperative CT-scans available. Baseline characteristics were collected, including gender, craniofacial surgical history, age at time of surgery, and time between preoperative CT-scan, MBD-RED, and postoperative CT-scan.

<u>Methodology</u>

A pipeline was created for the semi-automated 3D quantification of intrinsic bone and soft tissue changes following craniofacial surgery. All Digital Imaging and Communications in Medicine (DICOM)-files were converted to 3D bone and soft tissue meshes using Mimics Inprint 3.0. (Materialise NV, Leuven, Belgium). The 3D meshes were cleaned of redundant objects, such as draping and back of the CT-scanner. Bone meshes were further processed to isolate the MBD-RED surgical site (frontal bone, orbits, midface and zygomatic arch.) omitting the mandible and posterior calvarium from the mesh. The posterior calvarium was removed by a vertical plane cut approximately 1 cm posterior from the coronal sutures for the preoperative 3D bone mesh, and 1 cm posterior from the frontal bone osteotomy for the postoperative 3D bone mesh. The teeth were also omitted by making a mid-maxillary cut, as shown in Figure 1.c. (Meshmixer, Autodesk).

As this study aims to quantify the local bone and soft tissue changes following distraction. Postoperative 3D meshes were aligned (superimposed) on the preoperative maxilla. This stage removes any changes due to en-bloc advancement of the midface from the analysis, allowing the quantification to focus solely on the local changes of the bone and soft tissue. (Figure 2.) The alignment was achieved using a rigid iterative closest point registration (rigid ICP). To obtain this rigid ICP, the maxilla (i.e. area for alignment) was landmarked with 6 points using 3Matic software (Materialise NV, Leuven, Belgium), in which each point corresponded to the same anatomical point on the pre- and postoperative 3D mesh. (Figure 1a.) The same rigid transformation used to align the bone meshes was applied to the soft tissue, so that bone and corresponding soft tissue 3D meshes moved as a single entity.

The rigidly aligned meshes were then landmarked a priori to the non-rigid ICP registration used to obtain anatomical correspondence. Non-rigid registrations were performed using 8 landmarks for the soft tissue (right and left lateral canthi, right and left medial canthi, nose tip, right and left mouth corner, and chin), as shown in Figure 1.b and 18 skeleton landmarks (6 landmarks on the right and left orbit, and 3 on the right and left zygomatic arch), as shown in Figure 1.c). This anatomical dense correspondence was achieved using in-house code (Python Software Foundation).

Anatomical point-to-point distances were quantified and visualised using an arrow-map for the bone and a heatmap for the soft tissue, providing a clear and clinically valuable illustration of the outcomes. The arrows of the arrow map reflect the vector of the local bone displacements, from pre- to postoperative, of a particular anatomical point. The colours on the heatmap illustrate the absolute local soft tissue displacements as a result of the surgery. Changes of less than 2 millimetres (mm) were shown in green as they were considered negligible. As the nasal bone graft was not present in preoperative skeletal 3D meshes, anatomical dense correspondence could not be achieved in this area, and the bone graft was therefore omitted from the analysis. The results were compared with the conventional, closest point-to-point correspondence methodology, based on measurement of the distance between closest points, regardless of anatomical correspondence.

RESULTS

From an initial cohort of 27 patients, nine Apert Syndromic patients who had undergone MBD-RED met the inclusion criteria and were included in the construction and validation of the methodology. Eight patients underwent surgery at 17 +/- 4 years of age. An additional patient aged 2 years old was also included. A full overview is given in Supplemental Table 1. The median time between preoperative CT-scan and postoperative CT-scan was 477 days (range, 108 – 764), the median time between preoperative

CT-scan and MBD-RED (at time of insertion RED-frame), and MBD-RED and post-operative CT-scan was 158 days (range, 39 -566) and 198 days (range, 32 – 470), respectively.

The processing pipeline described in the methodology section was completed for all nine pairs of pre- and postoperative CT-scans in the dataset. The anatomical point-to-point distances for each study-subject at each of the landmarks are demonstrated in Supplemental Table 2-3.

Anatomical correspondence versus closest point-to-point registration

Figure 3. demonstrates a comparison of the anatomical point-to-point correspondence with the more common closest point-to-point correspondence in the two sample cases. The haphazard arrangement of the arrows clearly shows that the closest point-to-point correspondences do not accurately represent the true skeletal movements. Henceforth, the rest of the dataset underwent analysis using the anatomical correspondence.

Example case – Patient 7

Figure 4 reflects the pipeline for patient 7, a male Apert patient who had an MBD-RED at age 18. It gives an overview of our methodology that we applied to all cases. For illustrative purposes clinical photographs taken close to the CT-scan date were added to this figure. The initial rigid alignment on the maxilla is demonstrated for soft tissue (Figure 4.b) and bone (Figure 4.c), the green colour apparent on the maxilla reflects the superimposition on this region. From here, the next step was taken, a non-rigid alignment using the landmark set from Figure 1.c. The results from this non-rigid ICP are illustrated in Figure 4.e for soft tissue and Figure 4.f for bone. All above cases underwent this pipeline.

Local skeletal movements

The mean absolute displacements for the 18 landmarks for each patient were calculated as 3.3 mm (standard deviation (SD) 2.1 mm) for the mildest case (patient 1), 6.9 mm (SD 3.4 mm) for the average case (patient 7) and 12.8 mm (SD 7.3 mm) for the most severe case (patient 2). Landmarks 4,5,6 and 10,11,12 (right/left upper lateral orbital rim, superior orbital rim, and upper medial orbital rim, respectively) demonstrate the largest point-to-point movements. The zygomatic arches also underwent large point-to-point displacements with movements up to 17.8 mm observed at landmark 18 for patient 2 (Supplemental Table 2.). Four examples of the deformations and their direction of movement are shown as arrow maps in Figure 5. The local bone movements (after excluding the rigid midfacial advancements) show an overall upward and inward motion of the supraorbital rim, and a similar upward rotation of the zygoma. Overall, the arrows show an inward motion of the frontal bone, with displacements ranging from mild to severe over the cohort patients. Patient 2, the most severe case of the study-population, underwent the largest local movements from pre-to-postoperative state (Figure 5.).

<u>Soft tissue deformations in response to the skeletal movements</u>

The calculated displacements for the 8 soft tissue landmarks for each of the case studies is reported in Supplemental Table 2. Again, patient 1 was shown to undergo the mildest changes, and displacements of 2.5 mm and 4.6 mm for the right and left lateral canthus; 1.7 mm and 1.4 mm for the right and left medial canthi, respectively, were observed. For the average case, patient 7, this was calculated as 8.3 mm and 8.0 mm, and 11.0 mm and 4.6 mm of displacement for left and right lateral canthi, and left and right medial canthi respectively. As with the bone movements, the largest displacements were again observed for patient 2.

Although some of the largest local bone movements are seen in the zygomatic arch, the heatmaps show minor changes for the soft tissue in this region (Figure 5.). Thus, relatively large bone movements in the zygomatic arch do not directly translate to an equivalent change in the corresponding soft tissue. Figure 5. also demonstrates that certain areas, such as the cheekbone and peri-ocular region seem to translate in a different ratio from bone to soft tissue movement than other areas, such as the forehead, where a smaller ratio from bone to soft tissue movement is suggested.

For the most part, the largest soft tissue changes were observed at landmarks 1 and 4, i.e. the right and left lateral canthi, closely followed by the corresponding medial canthi. A larger degree of change was typically observed in the frontal bone; this is particularly evident with patient 2, the most severe case in the study cohort.

DISCUSSION

A semi-automated method was developed for the quantification of bone and soft tissue changes for craniofacial procedures. The constructed pipeline was applied to a dataset of 9 Apert patients who underwent midfacial bipartition distraction with RED-frame (MBD-RED). In order to quantify the intrinsic bone changes and corresponding soft tissue motion, the overall forward displacements achieved by the surgery and RED-frame distraction were omitted from the analysis. This was achieved by aligning the 3D bone meshes on the maxilla and applying the same transformation to the soft tissue so that both moved together. The maxilla was chosen as the alignment area for all pre- and postoperative 3D meshes, as this bone segment experiences the greatest displacement in terms of rigid advancement during midfacial bipartition distraction. Prior studies have also shown that the central part undergoes more distraction than the lateral areas. [8, 13] The maxilla therefore acted as a reference for the regions of interest for quantification of the local movement, i.e. the zygomatic arches, nasal bone, orbits, and frontal bone. After removal of the midfacial advancement, the largest deformations were observed in the upper lateral to medial orbital rim on the skeletal level which coincides with the aim of MBD-RED; namely to correct the hypertelorism and counterrotated orbits seen in Apert syndrome. This methodology provides information on the vectors of the skeletal differential movements, visualised in the arrow map. Due to different positioning of the mandible at time of pre and postoperative CT, this study did not describe displacements in this region.

The relationship between soft tissue and hard tissue movement varied. This might be due to various degree of decoupling of soft tissue as a result of dissection, ancillary procedures such as lateral canthopexy and midfacial suspension causing different shape changes postoperatively for bone as for soft tissue.

The time between pre- and postoperative CT-scans varied from 108-764 days, and factors such as growth may therefore have played a role in the final measurements and point-to-point correspondences described in Supplemental Table 2. At *Great Ormond Street Hospital for Children*, patients currently undergo a standardised pre-operative and follow-up CT scan protocol, consisting of a CT-scan module with high-quality imaging especially for craniofacial patients preoperatively, 1 week postoperatively and only in case of clinical concerns, a subsequent CT-scan as we aim to limit radiation as much as possible for our patient population. Many patients underwent MBD-RED prior to introduction of this standardised protocol and therefore did not have ideal CT-scans timings for the analysis of the bone and soft tissue movements. Others could not be included in this study due to the limited quality of the CT-scan for 3D reconstruction. Therefore, this study includes a relatively small number of MBD-RED cases that were performed at GOSH. The several patients that did meet the quality and inclusion criteria were less preferable in terms of CT-scan timings. The fact that surgery is performed at different ages and postoperative scans were performed at different intervals was a real challenge and from the point of view for this study has significantly downgraded the quality of the data. It is however a result of the GOSH philosophy on midfacial advancement. Midfacial advancement is performed only when there is a clinical need or the expectation of need for functional or psychological reasons rather than as a part of an age dependant reconstructive protocol. Similarly, late postoperative CT-scans are only undertaken to answer clinical questions in situations where they could alter management.

Literature suggests that the mean facial growth spurt corresponds to an age of 14.35 years for boys and 11.52 years for girls.[18] The majority of the subjects included in this study were beyond this growth peak and it is therefore unlikely that growth on its own played a large factor in the observed deformations. One case included in the analysis, however, was 2 years old at the time of MBD-RED and had 334 days between their pre- and postoperative CT-scans. The deformations quantified for this particular case were therefore not only due to the surgery but can also be attributed to skull growth during this period. As the CT-protocol is now in place, future studies could benefit from more timely quantification.

The proposed methodology uses the absolute distances (vectors) between corresponding points to display the deformation a heatmap. This is different from the approach presented in a prior study where 3 heatmaps were used per patient to illustrate the movements in the x (medio-lateral), y (vertical) and z (anterio-posterior) directions.[10] With this methodology the bone (arrow map) and soft tissue (heat maps) can be jointly considered to obtain a more intuitive understanding of the overall displacements.

In addition to solving functional issues this surgery also aims to 'normalise' the patient's appearance and address psychosocial problems. Thus, full understanding and quantification of shape changes resulting from surgery, together with a comparison of the soft tissue outcome of the treated patient with the normal facial shape, become essential to optimise the procedure. However, the normal face is not unique for a given individual, but actually falls within a wide range of acceptable shape features. A soft tissue model (Large Scale Facial Model, LSFM), based on approximately 10,000 normal individuals and quantifying the shape variations that occur in the normal population would allow this comparison.[19, 20] Indeed, Knoops et al. 2019 described how LSFM can be used to describe the surgical outcome of pre- to postoperative state after upper jaw (Le Fort I) surgery where the orthognathic patients were compared to an age matched group of normal peers.[20] Using a similar approach, the effect of MBD-RED for a cohort of patients in relation to an age-matched group of healthy peers could be analysed. The combination of a 3D understanding of the local tissue and bone movements provided by the presented methods, with an understanding of how results compare to the healthy LSFM population could play a role in a personalised and quantified treatment approach. In addition, not only could this approach be applied to MBD-RED, but the flexibility of the presented methodologies lends itself to applications for other types of craniofacial surgery, and could be used to facilitate real-time monitoring of a patient undergoing RED-frame distractive surgery at time of distraction. This would provide additional information about how the bone is moving in response to the RED-frame and allow for the opportunity to simultaneously adjust the distraction protocol accordingly. Moreover, in case sequential post-operative imaging is available, this methodology could be used to determine postoperative relapse in terms of the quantity and direction of the relapse. This information could, in turn, be used for surgical decision making and planning, and might influence the direction or quantity of distraction.

Ultimately, this methodology can give us accurate insight into the changes resulting from surgery regarding hard tissue and soft tissue. It does not provide us direct information on how to improve surgery. Yet, it gives us information to understand how shape changes have occurred which may lead to alterations in technique.

CONCLUSION

Local changes of the bone after midfacial bipartition distraction in Apert Syndrome are characterised by an upward inward rotation of the orbits, upward rotation of the zygoma and relative posterior motion of the frontal bone. The largest soft tissue movements are seen at the lateral canthi. However, no hard conclusions can be drawn given the varied cohort. Quantifications were performed in a semi-automatic manner. This new method has proven to be robust even for a cohort as varied as those with Apert syndrome and can be readily applied to other craniofacial abnormalities and surgeries, and used for the analysis of long-term surgical outcomes, including relapse. In the future, this method could also be used to enhance personalized surgical planning and guide RED-frame driven procedures in real-time.

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Conflict of interest

There are no conflicts of interest in the materials or subject matter dealt within the manuscript.

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REFERENCES

1. Tessier P. The definitive plastic surgical treatment of the severe facial deformities of craniofacial dysostosis. Crouzon's and Apert's diseases. *Plast Reconstr Surg*. Nov 1971;48(5):419-42.

2. Ortiz-Monasterio F, del Campo AF, Carrillo A. Advancement of the orbits and the midface in one piece, combined with frontal repositioning, for the correction of Crouzon's deformities. *Plast Reconstr Surg*. Apr 1978;61(4):507-16.

3. van der Meulen JC. Medial faciotomy. *Br J Plast Surg*. Oct 1979;32(4):339-42. doi:0007-1226(79)90095-X [pii]

4. Polley JW, Figueroa AA. Management of severe maxillary deficiency in childhood and adolescence through distraction osteogenesis with an external, adjustable, rigid distraction device. *J Craniofac Surg*. May 1997;8(3):181-5; discussion 186.

5. Tessier P. Facial bipartition: A concept more than a procedure. *Craniofacial Surgery*. Springer; 1987:217-245.

6. Shetye PR, Boutros S, Grayson BH, McCarthy JG. Midterm follow-up of midface distraction for syndromic craniosynostosis: a clinical and cephalometric study. *Plast Reconstr Surg*. Nov 2007;120(6):1621-32. doi:10.1097/01.prs.0000267422.37907.6f

7. Shetye PR, Davidson EH, Sorkin M, Grayson BH, McCarthy JG. Evaluation of three surgical techniques for advancement of the midface in growing children with syndromic craniosynostosis. *Plast Reconstr Surg*. Sep 2010;126(3):982-94. doi:10.1097/PRS.0b013e3181e6051e

8. Ponniah AJ, Witherow H, Richards R, Evans R, Hayward R, Dunaway D. Three-dimensional image analysis of facial skeletal changes after monobloc and bipartition distraction. *Plast Reconstr Surg*. Jul 2008;122(1):225-31. doi:10.1097/PRS.0b013e3181774308

00006534-200807000-00028 [pii]

9. Badiali G, Roncari A, Bianchi A, Taddei F, Marchetti C, Schileo E. Navigation in orthognathic surgery: 3D accuracy. *Facial Plastic Surgery*. 2015;31(05):463-473.

10. Almukhtar A, Khambay B, Ju X, Ayoub A. Comprehensive analysis of soft tissue changes in response to orthognathic surgery: mandibular versus bimaxillary advancement. *Int J Oral Maxillofac Surg*. Jun 2018;47(6):732-737. doi:10.1016/j.ijom.2017.11.014

11. Miller L, Morris DO, Berry E. Visualizing three-dimensional facial soft tissue changes following orthognathic surgery. *Eur J Orthod*. Feb 2007;29(1):14-20. doi:10.1093/ejo/cjl037

12. Amberg B, Romdhani S, Vetter T. Optimal step nonrigid ICP algorithms for surface registration. IEEE; 2007:1-8.

13. Greig AV, Britto JA, Abela C, et al. Correcting the typical Apert face: combining bipartition with monobloc distraction. *Plastic and reconstructive surgery*. 2013;131(2):219e-230e.

14. Shetye PR, Caterson EJ, Grayson BH, McCarthy JG. Soft-tissue profile changes following early Le Fort III distraction in growing children with syndromic craniosynostosis. *Plastic and reconstructive surgery*. 2013;132(4):945-954.

15. Visser R, Ruff CF, Angullia F, et al. Evaluating the efficacy of monobloc distraction in the Crouzon-Pfeiffer craniofacial deformity using geometric morphometrics. *Plastic and reconstructive surgery*. 2017;139(2):477e-487e.

16. Olate S, Zaror C, Mommaerts MY. A systematic review of soft-to-hard tissue ratios in orthognathic surgery. Part IV: 3D analysis–Is there evidence? *Journal of Cranio-Maxillofacial Surgery*. 2017;45(8):1278-1286.

17. Knoops P, Borghi A, Breakey R, et al. Three-dimensional soft tissue prediction in orthognathic surgery: a clinical comparison of Dolphin, ProPlan CMF, and probabilistic finite element modelling. *International journal of oral and maxillofacial surgery*. 2019;48(4):511-518.

18. Mellion ZJ, Behrents RG, Johnston LE, Jr. The pattern of facial skeletal growth and its relationship to various common indexes of maturation. *Am J Orthod Dentofacial Orthop*. Jun 2013;143(6):845-54. doi:10.1016/j.ajodo.2013.01.019

19. Booth J, Roussos A, Ponniah A, Dunaway D, Zafeiriou S. Large scale 3d morphable models. *International Journal of Computer Vision*. 2018;126(2-4):233-254.

20. Knoops PGM, Papaioannou A, Borghi A, et al. A machine learning framework for automated diagnosis and computer-assisted planning in plastic and reconstructive surgery. *Sci Rep*. Sep 19 2019;9(1):13597. doi:10.1038/s41598-019-49506-1

List of Supplemental Tables and figures