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CranioRate™: An Image-Based, Deep-Phenotyping Analysis Toolset and Online Clinician Interface for Metopic Craniosynostosis

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Abstract

Introduction

The diagnosis and management of metopic craniosynostosis involves subjective decision-making at the point of care. The purpose of this work is to describe a quantitative severity metric and point-of-care user interface to aid clinicians in the management of metopic craniosynostosis and to provide a platform for future research through deep phenotyping.

Methods

Two machine-learning algorithms were developed that quantify the severity of craniosynostosis – a supervised model specific to metopic craniosynostosis (Metopic Severity Score) and an unsupervised model used for cranial morphology in general (Cranial Morphology Deviation). CT imaging from multiple institutions were compiled to establish the spectrum of severity and a point-of-care tool was developed and validated.

Results

Over the study period (2019-2021), 254 patients with metopic craniosynostosis and 92 control patients who underwent CT scan between the ages of 6 and 18 months were included. Scans were processed using an unsupervised machine-learning based dysmorphology quantification tool, CranioRate^{TM}. The average Metopic severity score (MSS) for normal controls was 0.0±1.0 and for metopic synostosis was 4.9±2.3 ($p<0.001$). The average Cranial Morphology Deviation (CMD) for normal controls was 85.2±19.2 and for metopic synostosis was 189.9±43.4 ($p<0.001$). A point-of-care user interface (craniorate.org) has processed 46 CT images from 10 institutions.

Conclusion

The resulting quantification of severity using MSS and CMD has shown an improved capacity, relative to conventional measures, to automatically classify normal controls versus patients with metopic synostosis. We have mathematically described, in an objective and quantifiable manner, the distribution of phenotypes in metopic craniosynostosis.

Introduction

There is currently no objective, clinical tool for evaluating morphologic severity of craniosynostosis holistically. Previous research has evaluated the utility of severity metrics in metopic craniosynostosis, including inter-frontal angle,[1-5] lateral temporal width, and other craniometric measurements.[6-9] However, these metrics often require significant time, software and expertise to generate for each patient. They are also reductive - they do not consider the entire skull shape. Thus, they fail to capture the multidimensional variations in normal and pathological head shape which are relevant to treatment planning and prognosis.[10, 11] Furthermore, such low-dimensional craniometric measurements are non-intuitive for surgeons in that they typically measure cranial structures and parameters that are not directly useful for clinical decision making.[12-14]

Machine learning technology has increased in popularity in plastic surgery, with many potential applications that improve patient care.[15, 16] Precision medicine refers to treatments and diagnostic tools that are tailored specifically for individual patients such as using technology for preoperative planning and outcome analysis. Deep phenotyping is the result of precision medicine on a large scale and is defined as the precise and comprehensive analysis of phenotypic abnormalities in which the individual components of the phenotype are observed and described.[17] Deep phenotyping has become popular in basic science research, specifically in the field of genomics.[18, 19] However, clinical applications have also begun to apply deep phenotyping principles to previously unanswered clinical questions.[20, 21]

Several quantification algorithms for craniosynostosis have been proposed, yet there remains a need for automated, unsupervised processes and for large, multi-institutional collaborations.[22] Although pre-operative imaging is routinely employed to confirm the diagnosis

of craniosynostosis and aid in operative decision-making and planning, current methods to differentiate mild from severely affected individuals reduce complex three-dimensional shapes to unidimensional measurements that inadequately capture dysmorphology. As a result, limited data exists relating pre-operative severity to a broad range of clinical issues in these complex patients. Indeed, objective, quantitative deep phenotypes[17] of preoperative cranial morphology will empower clinicians with the ability to risk stratify their patients with craniosynostosis and thereby determine if, when, and how to intervene. Additionally, such deep phenotyping and subsequent analyses will allow for a more robust longitudinal assessment of surgical outcomes and facilitate collaborations between practices and institutions. Herein, we present severity data of a large population of patients with metopic craniosynostosis evaluated using CranioRate™, a point of care machine learning-based deep phenotyping tool.

Methods

Patient Inclusion

Under Institutional Review Board guidance, deidentified CT scans of patients with radiographically confirmed metopic craniosynostosis and normal control patients were collected from multiple institutions during the study period from 2019-2021. In addition, available postoperative CT scans were analyzed. Patients between the ages of 6 and 18 months were included. Patients with multiple-suture involvement were excluded. Patients with intracranial shunts and other external or internal hardware were excluded. Over thirty craniofacial and neurosurgeons were contacted regarding involvement in the study through data contributions to our image bank and beta testing of the point-of-care online portal.

Machine Learning Analysis

Each scan was processed using the CranioRate™ algorithm, which generates two unique severity scores: Metopic Severity Score (MSS) and Cranial Morphology Deviation (CMD). The MSS and CMD were developed and implemented as previously described.[23, 24] Each algorithm uses statistical shape modeling to quantify the deviation of skull shape from learned metopic and control shapes. MSS is specific to metopic synostosis and quantifies the severity of deviation from the normal head shape in the "metopic direction"; in other words, MSS quantifies the "metopic-ness" of a patient, where the score is scaled so that 0 represents an average normal control and 10 represents the most severely metopic patient in our dataset. By comparison, CMD is a non-specific measure of head shape that simply quantifies the deviation from normal in any direction. Descriptive statistics were presented for each distribution. Two-tailed independent t-tests were used to compare continuous data between distributions after normality was verified. An alpha of 0.05 was used for all statistical analysis. All statistics were generated using Stata SE 17 (College Station, TX).

Online Portal (craniorate.org)

The current implementation utilizes Amazon Web Services (AWS) infrastructure to record data that is uploaded to the website. The online portal performs several important quality assurance checks before processing the data: 1) confirm that the uploaded file is a CT scan, 2) confirm that the slice thickness is appropriate for analysis (maximum 2.3 mm slice thickness), 3) choose the image series with the greatest resolution. After the scan is uploaded, there is approximately one hour of processing time before the results are emailed to the user and displayed on the user's portal account. Alpha and beta testing of the CranioRate™ online portal (craniorate.org) were conducted over a two-year period (2020-2021) to evaluate the user interface and output metrics.

Results

Deep Phenotyping

Two groups of patients were analyzed in this study: normal control patients (n=92) and patients with metopic craniosynostosis (n=254). MSS is specific to metopic craniosynostosis with a maximum value of 10, where greater values indicate more severe patients. Normal controls were assigned a value of 0 and the metopic patients were linearly scaled so that the most severe patient is scored as a 10. A negative MSS value indicates a deviation from normal in the opposite direction as a metopic patient. **Figure 1** shows a sample group of six skulls, including one normal control patient and five metopic synostosis patients with MSS values ranging from 0 (least severe) to 10 (most severe). The average MSS for normal controls was 0.0 ± 1.0 and for metopic synostosis was 4.9 ± 2.3 ($p<0.001$).

CMD is non-specific and ranges from 0 to 300, with greater values indicating a more severe deviation from normal (in a non-specific direction). The average CMD for normal controls was 85.2 ± 19.2 and for metopic synostosis was 189.9 ± 43.4 ($p<0.001$). These results are summarized in **Table 1** and displayed graphically in **Figure 2**.

When evaluated together, the combination of MSS and CMD data provides a useful tool for the classification of various head shape pathologies based on the input CT scan. **Figure 3** displays three groups of patients graphically: normal controls, metopic craniosynostosis, and metopic patients postoperatively after fronto-orbital advancement (n = 54). Normal controls and patients with metopic craniosynostosis obey a linear relationship between MSS and CMD. Comparatively, postoperative patients (following FOA) have a large CMD but low MSS indicating they are "anti-metopic" in shape but still deviate significantly from normal (i.e. overcorrected).

Point of Care Implementation (craniorate.org)

The current CranioRate™ system has been beta tested and used to process 46 scans from 10 different institutions. Imaging data is deidentified before uploading to the online portal. Once an image has been uploaded, it takes approximately one hour for the scan to be processed through the algorithm. **Figures 4 and 5** show output display features that a user would receive on craniorate.org. **Figure 4** displays an interactive 3D rendering of the uploaded CT scan with a heat map that quantifies the spatial deviation from normal in these patients (inward, blue and outward, red). Users can virtually interact with these renderings on the portal. **Figure 5** shows a sample output from a scan with an MSS of 7.49. The graph displays the patient's severity among the histogram demonstrating scores from the population of 254 metopic scans and 92 normal control scans. **Figure 6** shows the steps of resampling, segmentation, and registration of the CT skull to the ShapeWorks model, which are also available as part of the output report on craniorate.org. These images can be useful to ensure data integrity by confirming that the scan maps sufficiently well to the sampling algorithm. The online portal currently only provides MSS data, not CMD.

Discussion

The aim of this study was to report the results from the deep phenotyping of a large cohort of patients with metopic craniosynostosis using a novel machine-learning algorithm to quantify head shape severity relative to the normal anatomical shape. There were statistically significant differences between scans from patients with craniosynostosis and normal controls for both MSS and CMD, validating our previous work that CranioRate™ effectively distinguishes between normal and pathologic with high accuracy. The primary result of this work, however, is a mathematically described distribution of head shape severity in patients with

metopic craniosynostosis. This has the potential to provide surgeons with a better understanding of the wide spectrum of dysmorphology and compare individual patients with the larger population.

Other algorithmic and machine-learning approaches have been developed but with drawbacks that impaired larger studies and widespread adoption. Furthermore, no previous work has attempted to deep phenotype metopic craniosynostosis using a large series of patient images, as we have presented in this study. For instance, Srivilasa et al[25] use a small set of manually placed landmarks, whereas the methods employed in this study utilize an automated system that analyzes the full 3D shape of the cranium. Several other methods, including those developed by Rodriguez-Flores et al.[26] and Lam et al.[27] among others[28] classify severity in craniosynostosis but require significant expert labor (cutting planes and landmarks) and often categorically define head shape rather than a continuous distribution. Ruiz-Correa at al.[29] also classify craniosynostosis type, but using features learned from the input data. Mendoza et al.[30] have previously performed a principal component analysis similar to the one used in this study, and they construct aggregate geometric features based on those differences. However, their model relied on a small sample size, and they have not performed any phenotypic distribution analysis. Lloyd et al.[22] present a survey of quantitative morphology in craniosynostosis and recognize (at that time) that challenges remain. They forecast "future directions will likely involve utilization of automated image registration, with techniques such as point set registration, along with computational strategies that measure cranial form in 3D." Indeed, this study precisely pursues these directions with the goal of bringing these approaches to wide-spread use through a robust, on-line, cloud-based tool that relies on analyses of large sets of normal and pathological examples.

Using our novel algorithm, decisions to operate can be precisely examined in the context of preoperative severity. This is crucial in examining the significant variation in the methods by which craniofacial surgeons decide whether to operate on a particular patient with craniosynostosis.[31, 32] A major limitation of implementing standardized protocols is the lack of objective quantification of severity. The Whitaker classification has been the gold standard for aesthetic outcomes reporting in craniosynostosis research,[33-36] but has been shown to have low inter-rater reliability and cannot predict the need for future interventions.[37] Most often, the decision is subjective and relies on surgical experience. Many clinical factors are considered, including patient age, comorbidities, type and severity of craniosynostosis, surgeon training and experience, aesthetic goals, future neurological complications, and patient family preference.[32] Furthermore, there are variations in the type of surgery offered to particular patients - open techniques, which have been the standard of care for several decades, and more recently developed minimally invasive techniques.[38] There is currently no agreed-upon objective method that contributes to surgical decision-making in the management of patients with craniosynostosis. Therefore, at the extremes of severity of craniosynostosis, in the mildest and most severe of cases, the decision whether to operate can be trivial for craniofacial surgeons. However, patients with moderate phenotypes are difficult to counsel and treat. Ultimately, especially in the age of precision medicine and patient-centered care, this tool could be used in conversations with patients/families to help them better understand the severity of their condition and provide perspective when discussing the decision to operate.

Furthermore, CranioRate^{TM} is unique in its multifaceted approach to severity quantification through two unique but related measures. MSS is a directional measure and quantifies the “metopic-ness” of a skull while CMD is non-directional and quantifies the

deviation of a skull from normal shape. The combination of MSS and CMD is a potentially powerful tool in evaluating postoperative changes in patients with metopic craniosynostosis (**Figure 3**). Normal controls and patients with metopic craniosynostosis obey a linear relationship between MSS and CMD, whereas postoperative patients deviate significantly from that trend. The CranioRate^{TM} tool provides new avenues to investigate postoperative results in craniosynostosis surgery. One long-debated clinical question, for example, is the appropriate degree of overcorrection that is required to achieve a normal head shape at long-term follow-up.[39] The further application and validation of CranioRate^{TM} for postoperative imaging may help quantify the degree of over-correction and allow for quantitative long-term analyses.

The online point-of-care tool, craniorate.org, has been in development for two years and has been through two rounds of testing and validation. Through feedback from craniofacial surgeons across the country, the automatic quantification feature has been reported to be particularly useful for craniofacial surgeons at the point of care and interesting and relevant to family discussions. These data currently augment family counseling and postoperative prognostication. In the future, we expect these tools to be analyzed in the context of clinical and radiographic outcomes in order to guide surgical decision making at the point of care.

Further future extensions of this work are underway. First, severity scores specific to sagittal and unicoronal synostosis will be developed similar to the MSS. Second, the algorithm is currently only validated for patients between the ages of approximately 6 and 18 months – we plan to extend the capabilities and validate the results on a wider range of patient ages. Finally, we plan to analyze postoperative imaging to evaluate the results of surgical correction on head shape over time, with the goal of quantifying overcorrection and subsequent regression towards a normal shape. This is particularly important since many institutions no longer perform routine

postoperative CT imaging due to the risk of radiation exposure and low diagnostic yield of such tests.[40] Indeed, current extensions of this work involve the quantification of craniosynostosis severity using 3D photography in place of CT imaging. While we have performed some initial studies on postoperative scans (**Figure 3**), CranioRate™ has not been validated to score the severity of such patients. One of the limitations of CranioRate™ is the broad age range of 6 to 18 months, which is a period of rapid head growth. The algorithm has been trained to score patients of all ages within this range, but we plan to further subsection the patients by age in future work to apply these data to clinical decision-making.

Conclusion

Using a novel machine learning algorithm with two unique measures of severity, we have performed the first deep phenotyping of a large cohort of patients with metopic craniosynostosis and have precisely defined the mathematical skull shape distribution in this population. There are many exciting future directions to build off this work and to continue to establish and contribute to our growing database of de-identified images.

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Figure Legends:

Figure 1: A group of six CT images and their resulting Metopic Severity Scores, including one normal (MSS = 0.18) and five metopic scans, in order of increasing severity.

Figure 2: Normalized distributions of severity in normal control scans and patients with metopic craniosynostosis in terms of Metopic Severity Score (top) and Cranial Morphology Deviation (bottom).

Figure 3: A scatter plot depicting the relationship between Metopic Severity Score and Cranial Morphology Deviation in three groups of patients: normal controls, metopic craniosynostosis, and postoperative scans following fronto-orbital advancement in patients with metopic craniosynostosis.

Figure 4: An interactive 3D rendering and heat map of a patient with metopic craniosynostosis that is generated for users on craniorate.org. The blue shading indicates deviation of the skull inward relative to normal and red shading indicates deviation of the skull outward relative to normal.

Figure 5: A sample output that would be generated for a user on craniorate.org with a patient whose Metopic Severity Score is 7.49. Among the 254 metopic craniosynostosis scans that have been collected, this score falls in the 65th percentile.

Figure 6: A schematic of the raw DICOM slices, resampling, segmentation and alignment of a sample patient's CT scan to the ShapeWorks skull model. These images are available to users in detail on craniorate.org and are useful for troubleshooting and data quality assurance in cases where inappropriate or poor-quality scans are uploaded to the online portal.

Table 1: Summary statistics of the patients who contributed to this work: normal controls and metopic craniosynostosis.

Table 1: Summary of Severity Metrics

Patients	N	Female (%)	Age (mean ± SD, months)	MSS (mean ± SD)	CMD (mean ± SD)
Normal Controls	92	42.4	13.2 ± 2.9	0.0 ± 1.0	85.2 ± 19.2
Metopic Synostosis	25 4	23.6	7.9 ± 3.6	4.9 ± 2.3*	189.9 ± 43.4*

* Indicates statistical significance from normal controls at $\alpha = 0.05$

Figure 1

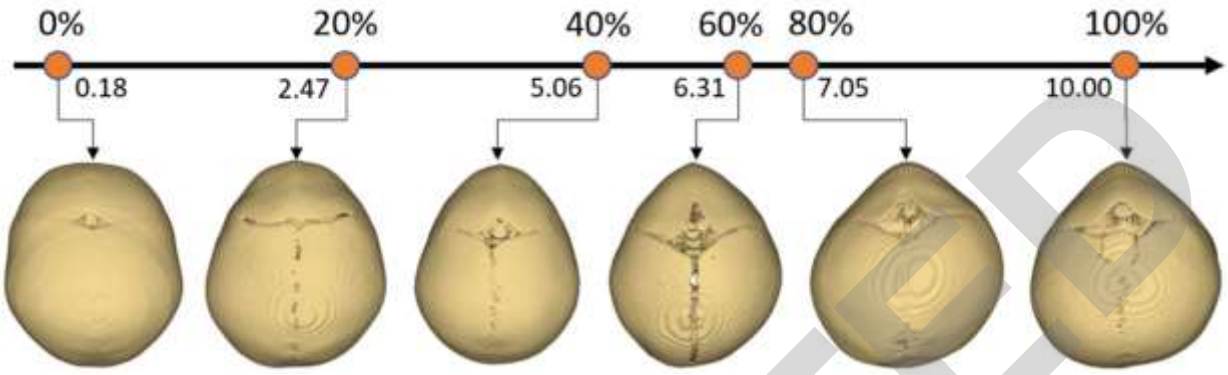

Figure 2

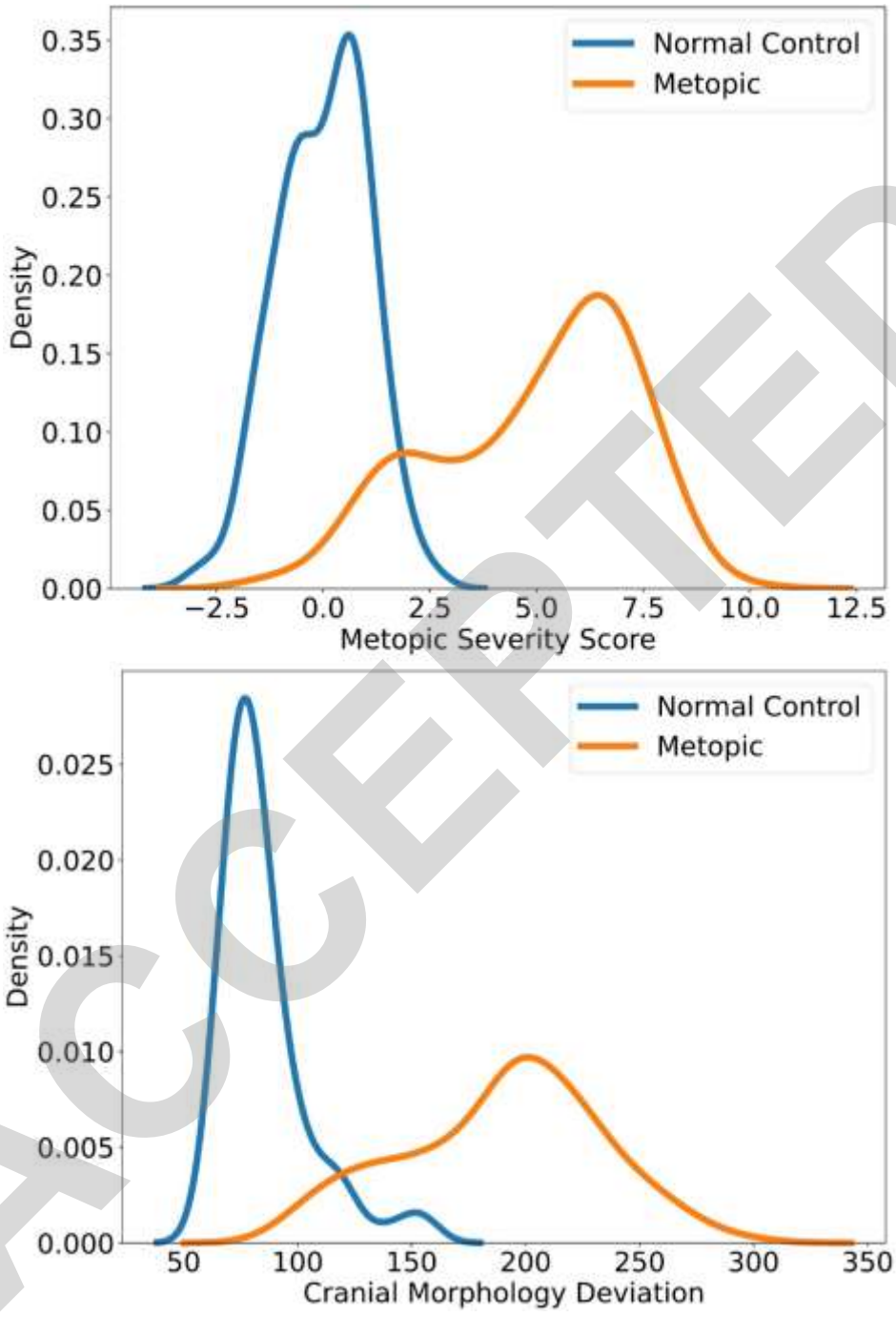

Figure 3

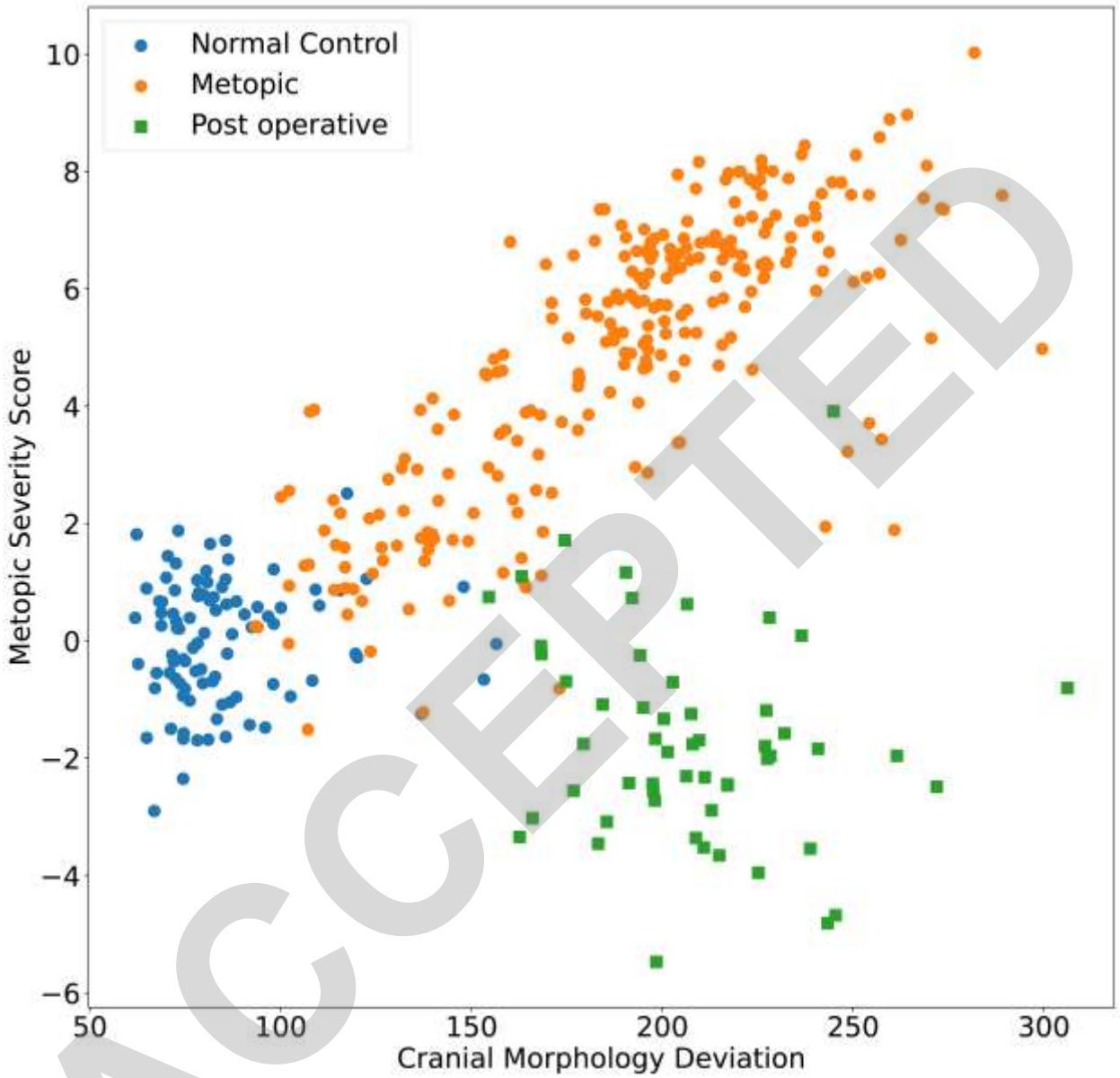

Figure 4

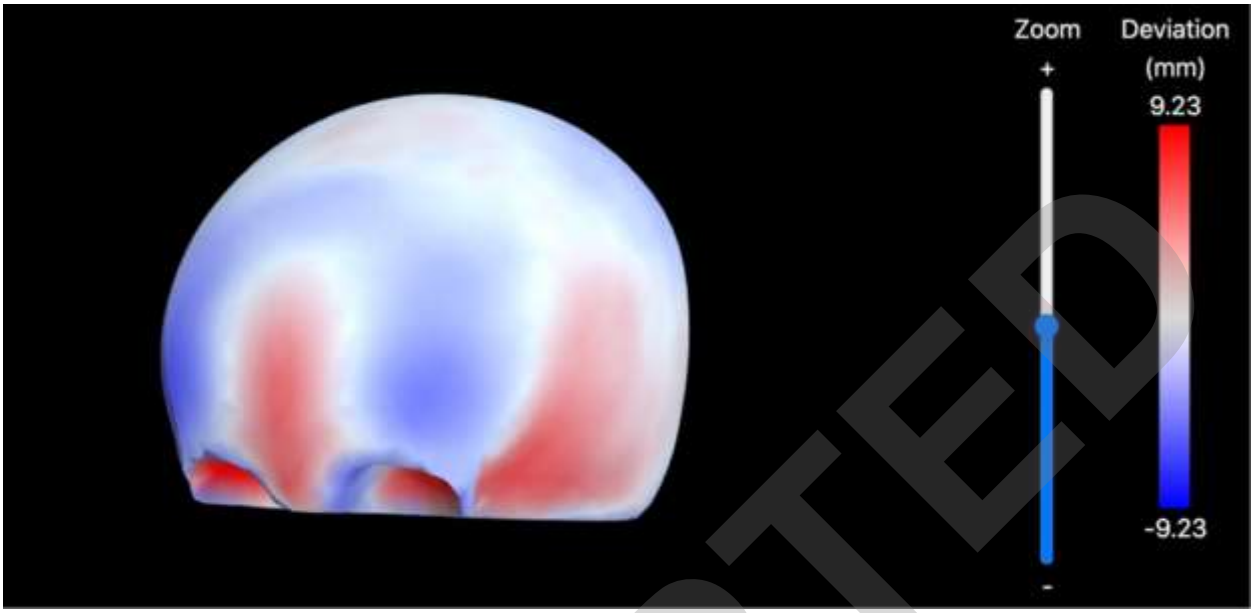

Figure 5

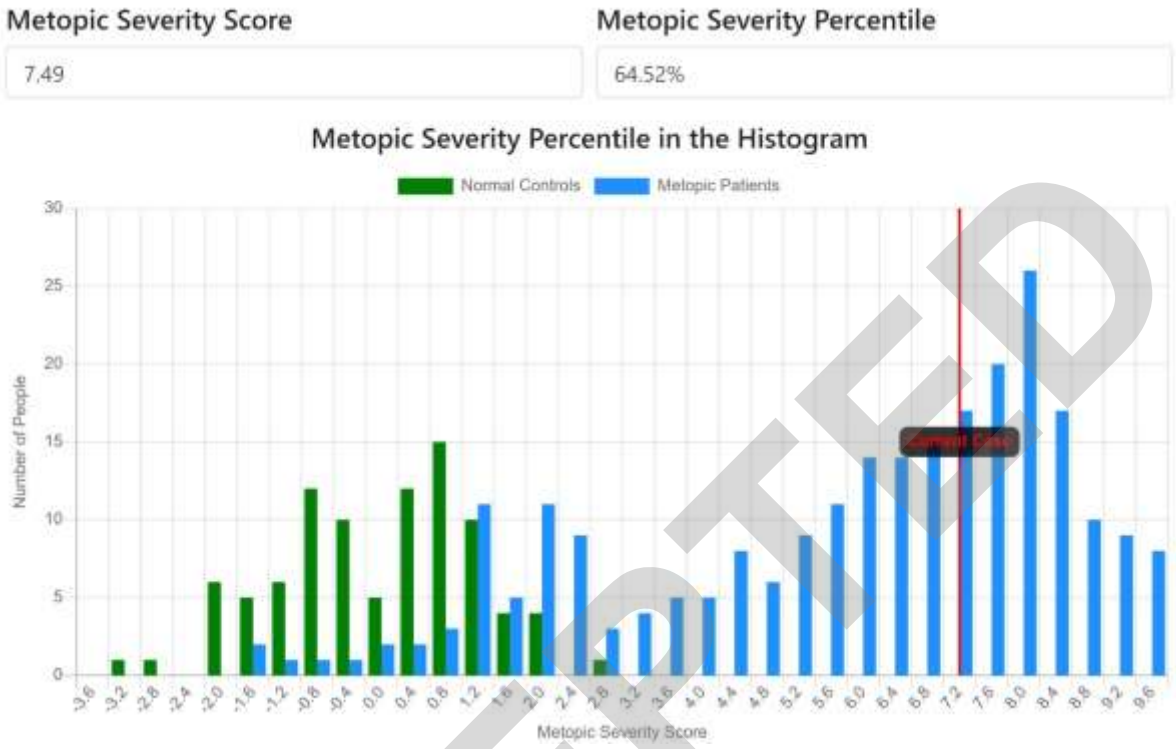

Figure 6