Novel Machine Learning Approaches to Examine Surgical

Outcomes in Patients with Craniosynostosis

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THESIS

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This thesis is dedicated to the Class of 2020 without whom none of this would have been possible. I am forever grateful to have you all in my life and for the three years we shared together.

#WBL

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LIST OF ABBREVIATIONS

AHRQ	Agency for Healthcare Research and Quality
ASA	American Society of Anesthesiologists
CT	Computerized Tomography
CVR	Cranial Vault Remodelling
DGA	Directive Growth Approach
DO	Distraction Osteogenesis
DS	Discharge Information Suppressed
HCUP	Healthcare Cost and Utilization Project
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICP	Intracranial Pressure
ICU	Intensive Care Unit
LOS	Length of Stay
NIS	Nationwide Inpatient Sample
NSQIP	National Surgical Quality Improvement Program
PDI	Pediatric Quality Indicators

SUMMARY

A novel machine learning approach was utilized for analysis of 8360 patients in the Nationwide Inpatient Sample (NIS) from the years 2012 to 2014. The dataset included patients under 3 years of age undergoing craniosynostosis repair surgeries and accounted for several patient- and hospital-level factors. The analysis sought to determine the associations between these factors and the occurrence of infectious complications, hospital costs, and length of stay.

The study showed that of the patients examined using the neural network model, 65% were male, 75% were under one year of age, the average age at admission was 0.4 years, 60% were white, 95% underwent elective surgery, and Medicaid and private insurance were approximately equal. Complication rate was 3.3%, mean length of stay was 4.3 days and overall hospitalization cost was $91,795. However, when differentiating between patients with and without an infectious complication, the mean length of stay with an infectious complication was 18.9 days compared to 3.8 without, and cost rose to $244,384 with an infectious complication compared to $86,490 without. The most relevant factors were determined to be comorbid burden, race, and non-elective procedure. Of the affecting comorbidities, neurological disorders, fluid and electrolyte disorders, and hypothyroidism present the highest risk.

High-risk cohorts for development of an infectious complication after craniosynostosis surgical repair, and therefore an extended length of stay and increased hospitalization costs, were identified. These patients are more likely to be non-White, between the ages of two and three, insured under Medicaid, having a non-elective procedure, with more than one comorbidity, the worst of which would be neurological disorders, fluid and electrolyte disorders, or hypothyroidism.

I. INTRODUCTION

A. Background

Craniosynostosis is the second most common craniofacial congenital defect in infants after cleft lip/palate. It is defined by premature fusion of cranial sutures and its prevalence is 1 in 2000-2500 live births. Multiple surgical interventions are required in these infants during the early years of life to repair the fused sutures, including cranial vault remodeling, fronto-orbital advancement, strip craniectomy, spring-assisted cranial expansion, and/or distraction osteogenesis.

B. Purpose of the Study

The purpose of this study is to examine a multitude of patient- and hospital-level factors associated with perioperative outcomes of craniosynostosis repair.

C. Significance of the Study

The analytical strategies utilized in this study are novel machine learning approaches which are able to discern patterns in large datasets. This innovative method can be further applied to build machine learning algorithms trained to analyze mass prospective clinical data. A continuous feedback loop allows the algorithm to constantly learn and improve its pattern recognition, generating outcome data that improves the quality of care in patients undergoing craniosynostosis corrections, and further applications to other fields of surgical specialty.

D. Null Hypotheses

1. The occurrence of infectious complications is not associated with longer length of stay in hospital and higher hospital charges.

2. A multitude of patient- and hospital-level factors are not associated with occurrence of infectious complications.

II. REVIEW OF THE LITERATURE

A. Introduction

Craniosynostosis is a congenital anomaly characterized by premature fusion of one or more cranial sutures before birth. Influenced by growth of the volume of the brain, sutural growth is the primary means of cranial vault expansion during the first 2 years of life (Mathijssen, 2015). Synostosis of the cranial sutures inhibits this necessary compensatory growth and causes malformations of the skull as well as functional deficits resulting from increased intracranial pressure (ICP). These effects can include optic atrophy, blindness, abnormal head shape or facial features, brain hypoplasia, hydrocephalus, developmental delay, reduced intracranial volume causing mental retardation, and in worst cases, death (Jeong et al., 2013). Reported symptoms of ICP are morning headache, recurrent vomiting, and developmental delay, but these are difficult to discern in infant patients (Derderian and Seaward, 2012). Unusual head shape evident before one year of age is the most common presentation (Johnson and Wilkie, 2011). Cephalocranial disproportion causes raised ICP, which increases exponentially with the number of affected sutures (Derderian and Seaward, 2012), and there is an increase in ICP of 15-20% of patients with multi-suture involvement compared to single-suture (Nguyen et al., 2013). Radiographs, funduscopic exam for papilledema, transorbital ultrasound, and visual evoked potentials are less invasive methods of diagnosis and monitoring of ICP (Derderian and Seaward, 2012).

Related to this, the downward displacement of the cerebellum through the foramen magnum is caused by ICP and is referred to as a chiari malformation. This symptom is common in craniosynostosis and occurs in 70% of Crouzon syndrome patients, 82% of Pfeiffer syndrome patients, and 100% of Kleeblattshadel syndrome patients (Derderian and Seaward, 2012). The incidence of craniosynostosis is estimated to be between 1 in 2000 to 1 in 2500 live births (Timberblake and Persing, 2018) (Mathijssen, 2015), and approximately 15% of these patients present as syndromic (Timberlake and Persing, 2018). Craniosynostosis is associated with more than 130 syndromes (Chattha et al., 2018), and syndromic patients

often have other associated comorbidities, birth defects, and the involvement of more than one suture (Mathijssen, 2015). As more advanced genetic data and improved research has become available, it is estimated that close to 60% of craniosynostosis cases are non-syndromic and 40% are syndromic (Mathijssen, 2015).

B. **Demographics**

Several studies have investigated the incidence and prevalence of craniosynostosis across different regions. In Western Australia, prevalence of craniosynostosis between the years of 1980-1994 was 5.06 per 10,000 births (Singer et al., 1999), similar to the prevalence of 4.3 per 10,000 in the metro-Atlanta area from 1989-2003 (Boulet et al., 2008). The Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project Kids Inpatient Database estimates prevalence of craniosynostosis at 3.5-4.5 per 10000 births between 1997 and 2006 (Nguyen et al., 2013). These values are lower than other studies in regions such as Colorado (14.1 per 10000), New South Wales (8.1 per 10000), and Israel (6.0 per 10000) for a coincident time period (Singer et al., 1999). The same study in Australia showed an increase in lambdoid synostosis of 15.7% per year linearly and did not determine a particular cause or explanation (Singer et al., 1999). Conversely, its metro-Atlanta counterpart discovered a decrease in prevalence of lambdoid synostosis and attributed this to a possible misclassification of deformational posterior plagiocephaly in these patients (Boulet et al., 2008). Demographic factors such as insurance, income, and race have an impact on age at the time of craniosynostosis surgery in the United States (Lin et al., 2015). Lin et al utilized the Kids' Inpatient Database in 2009 to determine that private insurance children were of 6.8 months mean age at the time of surgery while Medicaid children averaged 9.1 months old. White children averaged 7.2 months old, while Black and Hispanic children averaged 9.1 months old (Lin et al., 2015). Thus, Medicaid and nonwhite ethnicity were predictors for older age at surgery.

C. Syndromic vs. Non-Syndromic

Craniosynostosis can present in non-syndromic or syndromic form, and the diagnosis, risk factors, and management of these two groups differ. In non-syndromic cases, sagittal synostosis was most common followed by the lambdoid suture (Singer et al., 1999), while coronal suture involvement is more characteristics of syndromic craniosynostosis. Boulet et al found that 39% of non-syndromic cases involved sagittal synostosis, and that boys were more commonly affected while coronal synostosis was more common in girls. Male gender is also a risk factor for lambdoid synostosis (Boulet et al., 2008). While less severe, it is important to note that other major birth defects were still noted in 11.2% of non-syndromic patients (Singer et al., 1999). Non-syndromic patients develop cranial deformities due to growth restriction at the synostosed suture and compensation at the normal sutures (Mann et al., 2017). Syndromic craniosynostosis is notably more complex, harder to care for, and necessitates multidisciplinary treatment. It is also associated with an increased risk of elevated intracranial pressure due to intracranial venous congestion, hydrocephalus, and upper airway obstruction (Derderian and Seaward, 2012). Syndromic patients are at the greatest risk for perioperative complications (Bruce et al., 2018). Diagnosis of a syndrome is based primarily on dysmorphologic presentation and genetic testing (Mathijssen, 2015), and Singer et al found that 25.3% of craniosynostosis patients in their study were seen by a geneticist (Singer et al., 1999).

Several syndromes have craniosynostosis involvement. These include Crouzon, Apert, Pfeiffer, Saethre-Chotzen, and Muenke. The most common syndromes are Muenke, followed by Crouzon, Pfeiffer, then Apert (Mathijssen, 2015). Patients with Crouzon's syndrome present most commonly with bicoronal synostosis, brachycephaly, shallow orbits with ocular proptosis, midface hypoplasia, and anterior open bite; it is estimated to affect 1 in 25000 live births (Derderian and Seaward, 2012). Crouzon's patients have orthodontic problems related to maxilla deficiency in vertical, transverse, and sagittal dimensions (Kreiborg, 1981). Apert's syndrome is similar in presentation with more severe midface hypoplasia, characterized additionally by syndactyly, and affects 1 in 65000 live births (Derderian and Seaward, 2012). Apert's syndrome is characterized by more than a 1-year delay in dental development as well as delayed

eruption of the teeth, crowding of upper teeth, and skeletal discrepancy between the upper and lower jaws (Kaloust et al., 1997). Boulet et al estimate that 40% of syndromic cases of craniosynostosis have the diagnosis of Apert's syndrome (Boulet et al., 2008). Patients with Apert's syndrome present with reduced maxillary growth and airway restriction resulting in mouth breathing and open bites, and therefore orthodontic intervention during growth could reduce the impact of the developing dentofacial deformities (Letra et al., 2007). Pfeiffer syndrome involves the same midface hypoplasia and syndactyly, as well as broad thumbs and big toes, hypertelorism, downslanting palpebral fissures, strabismus, class III malocclusion, and beaked nasal deformity (Derderian and Seaward, 2012). It is even rarer with an incidence of 1 in 100000 live births and appears in 3 types with increasing severity. These patients have a higher likelihood of conductive hearing loss, aural atresia, hydrocephalus, tracheostomy, and Chiari malformation (Derderian and Seaward, 2012). Saethre-Chotzen syndrome is characterized most often by bicoronal synostosis, presence of ptosis, a low frontal hairline, and ear deformities without midface hypoplasia. Muenke syndrome involves hearing loss, developmental delays, and thumb-like middle phalanges with the absence of midface hypoplasia. The incidence of these two syndromes is 1 in 25000-50000 births and 1 in 10000, respectively, and both incur high reoperation rates of cranial vault expansion (Derderian and Seaward, 2012).

D. **Genetics**

The genetic component of craniosynostosis is quite significant. Johnson & Wilkie noted that 21% of craniosynostosis cases had genetic diagnosis of single gene mutations or chromosomal abnormalities (Johnson and Wilkie, 2011). Timberlake and Persing state that non-syndromic craniosynostosis is sporadic in 95% families, but previous genetic panels were of low diagnostic utility. Furthermore, adequate genomic sequencing has been limited by cost and small sample sizes at any one center , possibly reducing the known significance of the genetic component to craniosynostosis presentation (Timberlake and Persing, 2018). The Johnson & Wilkie study states that craniosynostosis presents most commonly in the sagittal suture, followed by coronal, metopic, and lambdoid sutures. Notably, this study mentions environmental factors

such as intrauterine fetal head constraint as well as genetics (single gene mutations, chromosome abnormalities, polygenic background) predisposing for craniosynostosis (Johnson and Wilkie, 2011). Genetically, the craniosynostosis condition is mostly of autosomal dominant inheritance and multi-suture involvement and extracranial complications are often associated. The most common genes mutated are FGFR2, FGFR3, TWIST1, and EFNB1 (Johnson and Wilkie, 2011). Crouzon, Apert, and Pfeiffer syndromes are caused by mutation to the FGFR-2 gene, Saethre-Chotzen is caused by the TWIST-1 gene mutation, and Muenke is uniquely affected by the FGFR-3 gene mutation (Derderian and Seaward, 2012). In a study by Timberlake and Persing, exome sequencing was completed in 384 families and a new genetic testing protocol was established. They determined that syndromic craniosynostoses are affected by FGF/Ras/ERK, BMP, Wnt, ephrin, hedgehog, and STAT genes, as well as resultant deficits in the retinoic acid signaling pathways (Timberlake and Persing, 2018). While not as apparent in genetic basis as syndromic craniosynostosis, non-syndromic craniosynostosis displays a non-Mendelian inheritance pattern but still frequently involves mutations in the Wnt, BMP, and Ras/ERK pathways (Timberlake and Persing, 2018). Another study by Wilkie et al utilized targeted molecular genetic and cytogenetic testing for 326 children born between 1993-2002 that required craniosynostosis repair surgery, and they discovered that a genetic diagnosis was achievable in 21% of cases and was associated with an increased risk of complications (Wilkie et al., 2010). Therefore, genetic workups are integral to the management of craniosynostosis patients and contribute to both risk assessment and overall prognosis (Johnson and Wilkie, 2011). Screening of non-syndromic cases of sagittal and metopic craniosynostosis for SMAD6 mutations is recommended; non-syndromic coronal synostoses should be screened for TCF1 or TWIST1 mutations, as well as the FGFR3 P250R variant which is associated with Muenke syndrome (Timberlake & Persing, 2018) (Wilkie et al, 2010).

E. **Surgical Intervention**

There are several surgical techniques employed in the repair of craniosynostosis. A landmark study completed by Mathijssen in 2015 published guidelines for all aspects of non-syndromic and syndromic

craniosynostosis care in the Netherlands; they state that the aim of treatment is to enlarge cranial volume to prevent ICP and correct shape of cranium, orbit, and maxilla (Mathijssen, 2015). While the ultimate aim of surgery is to increase intracranial volume and restore normal head shape (Derderian and Seaward, 2012), in severe cases the goals of treatment are simply to maintain airway, support adequate feeding, protect the eyes, and treat intracranial pressure (Johnson and Wilkie, 2011). In terms of protocol for diagnosis, a study by Chim & Gosain found that 75% of craniofacial surgeons surveyed agreed that CT was not required before surgery, and CT scans were only used when the physical exam was unclear for diagnosis. While ultrasonography was proposed as a viable alternative, it was only shown to be accurate up to 12-13 months of age, after which sutures narrow and bone thickens (Timberlake & Persing, 2018). Age is an important factor for timing of repair, particularly in this cohort of young infants as so much growth and development occurs before the age of one. The cranial bones are quite malleable but too weak to support rigid fixation methods when a child in less than 6 months old, which may limit surgical options. However, the bone is thicker and allows for adequate rigid fixation once patients are one year old, but reshaping ability is compromised (Derderian and Seaward, 2012). The general consensus is that corrective surgery should occur prior to the age of 1, ideally between 6-9 months old, and common techniques include anterior cranial vault remodeling (CVR), posterior cranial vault expansion, distraction osteogenesis (DO), or spring-assisted cranioplasty (Derderian and Seaward, 2012).

Strip craniectomy is deemed less invasive, while CVR allows for improved correction and release of brain compression which positively influences brain development, implicated in long-term neurocognitive function (Wu et al., 2018). Decompressive strip craniectomies may be employed for early-onset increases in intracranial pressure, sometimes in infants younger than 3 months of age, and are followed by spring-assisted cranioplasty between the ages of 3-6 months (Derderian and Seaward, 2012). Posterior cranial vault remodelling allows for volume expansion and improved head shape. The posterior CVR showed increased blood loss compared to anterior CVR, limited advancement by soft tissue coverage, and relapse was more common due to the weight applied when the infant lies down (Derderian and Seaward,

2012). Conversely, posterior vault distraction osteogenesis has been shown to maintain bone vascularity, limit production of dead space in the cranial vault, as well as expand the soft tissue envelope more gradually. This procedure requires a second surgery for device removal, which directly prolongs treatment time, associated morbidity, and complications related to the distraction device. Both posterior CVR and posterior distraction displayed improvement in cerebellar anatomy, also described as successful decompression in the region of the Chiari malformation (Derderian and Seaward, 2012). Spring-assisted cranioplasties are less common and usually used in sagittal synostoses, utilizing a continuous force across an osteotomy. They exhibit lower morbidity than open surgical procedures and require shorter operative time, but share a similar downside to distraction osteogenesis in that a second procedure is required for device removal, but with even less control of treatment outcome than DO (Derderian and Seaward, 2012). Lastly, fronto-orbital advancement surgically expands the anterior skull to increase volume, improve shape, and advance retruded orbits for better aesthetics (Derderian and Seaward, 2012). A new technique is proposed by Mann et al. named the directive growth approach (DGA), which temporarily restricts growth in areas of overcompensation and forces growth in the region of previous synostosis to preserve a normally functioning suture for improved future cranial growth, while reducing operative time and blood loss (Mann et al., 2017).

In terms of growth effects, patients with sagittal synostosis who had strip craniectomy or CVR showed resultant altered growth of the cranial base. This is described as increased mediolateral growth, greater anteroposterior expansion of anterior cranial fossa, and decreased growth in posterior cranial fossa (Chim and Gosain, 2011). Reoperation is common with all procedures in syndromic cases; these patients show more frequent signs of ICP, ocular symptoms, and poorer functional and aesthetic results in the long-term (Derderian and Seaward, 2012). Chim & Gosain, assessed some of the aforementioned techniques and it was found that spring-mediated cranioplasty was as effective as modified pi-plasty for non-syndromic sagittal synostosis repair. Fronto-orbital advancement and cranial vault remodelling procedures that were performed between the ages of 4-13 months were examined, and there was no difference in orbital growth between fixation techniques of miniplates versus sutures (Chim and Gosain, 2011). Overall, less blood

replacement was required and there was significantly shorter postoperative anesthesia necessitated while hospital stays were reduced (Chim and Gosain, 2011). In a survey of 53 surgeons, Alperovich et al. found that one quarter prescribe extended course antibiotics after craniosynostosis repair, two-thirds utilize blood transfusions in 76-100% of their operations, and 93.6% send patients to ICU (Alperovic et al., 2015). The majority of surgeons implement appropriate safety precautions, but differences in practice patterns may alter patients in terms of radiation exposure via diagnostics, antibiotic protocols, blood transfusions, and overall health expenditures (Alperovic et al., 2015). The study concluded that there was no consensus on pre-operative, intra-operative, and post-operative practice patterns for intracranial reconstruction (Alperovic et al., 2015). Some research suggests that perioperative steroid administration decreases facial edema, ecchymosis, pain, and reduces length of stay (Wei et al., 2015). A systematic review by Wei et al. assesses patients receiving perioperative steroids in open CVR and results showed earlier eye opening, improved post-operative edema, and reduced length of stay (Wei et al., 2015).

The two most common surgical interventions are strip craniectomy and cranial vault remodelling (CVR). Wu et al. investigated the socioeconomic disparities, associated costs, and complication rates between these two procedures with a sample of 251 patients undergoing strip craniectomies and 1811 patients undergoing CVR in the United States between 2000-2009 using the Kids' Inpatient Database (Wu et al., 2018). They found that more of the strip craniectomy patients had private insurance while Medicaid coverage was more common for CVR patients. Geographically, strip craniectomies were more common in the West and Midwest, while CVR was more common in the South. Overall, perioperative charges averaged $27,962 more with CVR than with strip craniectomies, but postoperative complications were equivocal despite CVR having more accidental puncture and serum transfusion incidents. It is important to recognize the widening socioeconomic disparities between the procedures, CVR being more common among minority groups and patients with Medicaid compared to strip craniectomy which is more common among the White population with private insurance (Wu et al., 2018). It was discovered that CVR had decreasing length of stay and a higher safety profile. Strip craniectomy has lower immediate cost and fewer short-term

complications (Wu et al., 2018). A systematic review of short- and long-term outcomes in single-suture coronal, metopic, and lambdoid craniosynostosis suggests that the less invasive craniectomy techniques may be superior to CVR in non-sagittal craniosynostoses as well (Bennett et al., 2019). Prior research noted that patients of minority groups had delayed craniosynostosis diagnosis and therefore later surgery, leading to an increased perioperative hospital charges of $10000-14000 among non-white patients. These patients present too late for strip craniectomy and are limited by the only possibly option of CVR and its associated benefits and drawbacks (Wu et al., 2018). A retrospective cohort study compared the cost-effectiveness of open CVR in 17 patients versus endoscope-assisted repair in 16 patients for sagittal suture craniosynostosis and found that open CVR required more operating room time, more days in the ICU, more blood transfusions, and was 73% more expensive overall (Liles et al., 2019).

F. **Complications**

The definition of perioperative and postoperative complications varies between the numerous studies investigating craniosynostosis, such as adverse events requiring changed management (Lee et al., 2012) or prolonged hospitalization, readmission, reoperation, or mortality (Pearson et al., 2008). In specific reference to craniosynostosis repair, procedures have become exceedingly complex over time which has resulted in increased complication but better outcomes (Lee et al., 2012). Rates of complications from these procedures range in Western literature from 3.3%-36% (Jeong et al., 2013). Bruce et al states that the risk of complications increases with age and therefore the optimal time for surgical repair is prior to one year to reduce risk and the resultant increased cost and length of hospital stay (Bruce et al., 2018). Complications compromise quality of life and increase health care costs overall (Prakasam et al., 2016).

Studies have found that overall complication rates between strip craniectomy and CVR procedures were comparable. There were higher serum transfusion rates with CVR as well as high rates of accidental puncture which is consistent with the longer and more invasive operation (Wu et al., 2018). In a study by Esparza and Hinojos reviewing 306 transcranial procedures between 1999 and 2007, it was found that the

lowest complication rates occurred in the less-invasive endoscopic-assisted osteotomies, while the highest occurred with complete CVR in scaphocephalies and multiple synostoses, which is a very complex surgery (Esparza and Hinojosa, 2008). The most frequent complications in the study were postoperative hyperthermia, infection, subcutaneous hematoma, dural tears, and cerebrospinal fluid leakage, and these were found to be higher among reoperation patients (Esparza and Hinojosa, 2008). Timing of surgery and the use of fronto-orbital advancement procedures were examined across 6010 patients in the National Inpatient Sample (NIS) from 1998-2009 as predictors of post-operative complications (Abraham et al., 2018). While syndromic patients and those receiving blood transfusions had higher complication rates, it was found that surgery at age 7-12 months and having a fronto-orbital advancement were also predictors for complications (Abraham et al., 2018). A retrospective study by Han et al. compared complications in 295 non-syndromic and 33 syndromic patients undergoing CVR versus endoscopic techniques over 10 years, investigating age, skin incision method, blood loss, transfusion, steroids, procedure length, and length of stay (Han et al., 2016). They stated that endoscopic procedures had less blood loss, shorter procedure length, and shorter length of stay, but complication rates were found to be equal between both techniques (Han et al., 2016).

Complication rates have been shown to vary and are affected by hospital type, region, and volume. Chatta et al. explored the relationship between hospital volume, complications, and resource utilization in non-syndromic children under 1 year of age undergoing craniosynostosis repair across 154 hospitals of varying size in the United States (Chattha et al., 2018). The outcomes measured were major complications, blood transfusions, hospital charges, and length of stay; blood transfusions were highest at low volume hospitals while length of stay and costs were lowest at high volume centers. It was determined that hospital volume was associated with significant differences in patient comorbidities, geographic region, and race, in that Black and Hispanic patients were less likely to be treated at high volume hospitals where increased surgical volume correlated with better surgical outcomes and lower postoperative complications (Chattha et al., 2018). The National Inpatient Sample (NIS) data set from 2003-2010 accounts for 19,417 patients

under the age of 3 undergoing craniosynostosis repair surgeries and shows an increase in regionalization to major teaching hospitals from 83.3% to 97.5% over those 8 years (Allareddy, 2016). Currently greater than 97% of craniosynostosis surgery is performed at major academic centers across the United States (Chattha et al., 2018), but the effect of regionalization is unknown (Allareddy, 2016). Higher complication rates are more common at teaching hospitals than non-teaching hospitals, likely due to increased case complexity (Prakasam et al., 2016).

A study by Allareddy examined the association between complications and hospitalization outcomes in surgical repair of craniosynostosis using 17,788 cases in the NIS from 2004-2010 (Allareddy, 2014). These complications included non-healing wounds, hemorrhages, infections, iatrogenically induced complications, respiratory complications, nervous system complications, and cardiac complications which were correlated with higher hospital charges (Allareddy, 2014).While these complications occurred in less than 1% of patients, they were strongly associated with poor outcomes (Allareddy, 2014). Additionally, longer hospital stays were related to septicemia, bacterial infections, mycoses, hemorrhage, other infections, iatrogenically induced complications, vascular complications, digestive system complications, nervous system complications, and postoperative pneumonia (Allareddy, 2014). It was found that 10.1% of patients had increased hospitalizations related to complications, most commonly hemorrhage (4.1%), iatrogenically induced complications (accidental punctures, lacerations, pneumothorax 3.1%), cardiac complications (0.7%), bacterial infections (0.7%), and respiratory complications (0.7%) (Allareddy, 2014). When Lee et al. reviewed over 30 years of craniosynostosis repair surgeries and assessed complications across 796 patients, they found that the predictors of complications were multi-suture involvement, syndromic cases, patients under 9 months of age, spring-assisted cranioplasty procedures, longer surgeries, and higher numbers of blood transfusions (Lee et al., 2012). Of these, multi-suture and syndromic cases were correlated with recurrent stenosis, which may be due to less favorable bone quality, larger alterations in head shapes, increase in preoperative ICP, genetic factors, or other anomalies such as airway obstruction (Lee et al., 2012). Nguyen et al. examined perioperative outcomes of craniosynostosis repair across United States

community hospitals through the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project Kids Inpatient Database in the years 1997, 2000, 2003, and 2006 (Nguyen et al., 2013). The data set included 3426 patients, the majority of whom were white males and insured, 98% of which were treated in teaching hospitals and 99% were in urban centers (Nguyen et al., 2013). They found that 10% of patients had acute complications like hemorrhage, hematoma, or respiratory failure (Nguyen et al., 2013).

Several other studies have utilized the NIS data set, including that of Prakasam et al. which reviewed facial reconstructive procedures between 2004-2010 to assess the prevalence and predictors of complications (Prakasam et al., 2016). It was found that 20% of procedures had a complication: postoperative pneumonia (4.9%), hemorrhage (3.9%), other infections (3.6%), non-healing wounds (3.5%), and iatrogenically induced (3.2%) (Prakasam et al., 2016). A study by Allareddy et al. explored the NIS database from 2009 and 2010 for surgical lymph node excision procedures, assessing prevalence and impact of adverse effects of medical care in 48413 hospitalizations (Allareddy et al., 2014). It was found that adverse effects occurred in 9.5% of cases, and complications were defined as postoperative pneumonia, hemorrhagic complications, other infections, cardiac complications, bacterial infections, respiratory complications, non-healing wounds, septicemia, or mycoses (Allareddy et al., 2014). They concluded that errors of execution and planning contribute to medical errors and thus the resultant complications (Allareddy et al., 2014). The benefit of using the NIS dataset is that the hospitals are nationally representative, making it generalizable and externally valid (Allareddy, 2014). In addition, single-center studies reflect only the outcome patterns of that particular institution, whereas national datasets account of rare events and produce more representative estimates (Allareddy, 2014).

However, valuable investigations have occurred outside the United States including a single-center review of 96 cases from 1996-2009 at Seoul National University Children's Hospital (Jeong et al., 2013). This study accounted for age at the time of surgery, operative time, and length of stay, in comparison to the amount of blood loss, signs related to increased ICP, aesthetic results, and complications (Jeong et al.,

2013). This data was compared to the results of a 10-year past study from 1986-1995 at the same hospital, and it was found that signs related to ICP were improved, papilledema and ventriculomegaly decreased, reoperation rates were low, good aesthetic results were observed and most importantly, complications decreased from 66.7% to 29.2% (Jeong et al., 2013). Over the 14-year gap it was found that diagnosis and surgery occurred earlier, and there was a significant reduction in morbidity and length of stay as a result of decreased operative time (Jeong et al., 2013). The authors concluded that the most important factor was the experience level of the plastic surgeons and interdisciplinary planning with experienced neurosurgeons and anesthesiologists (Jeong et al., 2013). The main factor in low mortality rates is likely a well-organized interdisciplinary team (Nguyen et al., 2013).

G. **Risk Factors and Outcomes**

Risk factors for craniosynostosis are varied and vast. Several studies list factors such as being male or preterm birth (Singer et al., 1999) (Boulet et al, 2008), maternal age is over 35, multiple births (Boulet et al., 2008), fetus breech, or fathers of an age over 40 (Singer et al., 1999). A study by Prakasam et al. found that the risk factors influencing complication rates were age, comorbid burden, and sex; additionally, increase in age and comorbid burden were significantly associated with increased risk of development of multiple complications (Prakasam et al., 2016). Risk factors linked to the need for blood transfusion are lung injury, acute hemolytic reaction, and infectious disease transmission (Alperovic et al., 2015). Lam et al. utilized the National Surgical Quality Improvement Program (NSQIP) Pediatric sample to describe 30-day outcomes, perioperative events, and rates of blood transfusion over 572 surgeries (Lam et al., 2016). Average length of stay was 4.22 days, 67% of patients received blood transfusions, 3.15% experienced perioperative infection, unplanned reintubation, cardiac arrest, wound disruption, stroke/hemorrhage, seizures, or thromboembolism, and 2.8% of patients were readmitted while 2.45% underwent reoperation within 30 days (Lam et al., 2016). Age of the patient is relevant, and while craniosynostosis surgery is safe, the increased length of stay is associated with comorbidities in patients aged 1-3 years (Nguyen et al., 2013). Longer length of stay can double hospital charges and patient costs (Nguyen et al., 2013). It has been

questioned whether hospital volume impacts craniosynostosis repair outcomes. Wes et al. utilized the Pediatric Health Information System of 13000 patients across 49 institutions from 2004-2015 to compare patients undergoing repair at high volume institutions seeing more than 40 cases per year, or low volume institutions seeing less than 40 (Wes et al., 2017). Outcomes included complications, length of stay, and increased cost, and it was found that high volume centers had decreased odds of complications, decreased length of stay, and lower costs (Wes et al., 2017).

The same NSQIP data set from 2012-2014 was investigated by Jubbal et al. to determine short term 30-day reoperation rates, unplanned readmission rates, and the overall morbidity of craniosynostosis repair surgeries of 2037 patients (Jubbal et al., 2017). They defined morbidity as the occurrence of pneumonia, wounds, sepsis, renal and urinary complications, venous thromboembolism, cardiac complications, or nerve injury, and discovered that reoperation rate was 2.4%, morbidity was 2.8%, and readmission rate was 3.4% (Jubbal et al., 2017). Risk factors for reoperation included a high ASA classification of 3 or 4 which was correlated with unplanned 30-day readmission, and a history of neurologic disorders which was associated with overall morbidity. The most common reason for readmission was wound and respiratory complications (Jubbal et al., 2017). The study found that there were no appreciable associations with outcome and blood disorders, cardiac risk factors, gender, or prior operation (Jubbal et al., 2017). Bartz-Kurycki et al. also utilized the NSQIP data set for patients with and without cardiac risk factors to analyze postoperative complications from CVR because 8% of patients with craniosynostosis also have congenital cardiac malformation (Bartz-Kurycki et al., 2019). They discovered that two thirds of the patients experienced a complication, most commonly bleeding requiring transfusion, and concluded that patients with cardiac risk factors have more complications (Bartz-Kurycki et al., 2019). Single-center studies have performed retrospective assessments of the outcomes of CVR procedures. Seruya et al. reviewed 212 patients and found a 3.3% complication rate including cerebral contusions, hematomas, cerebrospinal fluid leak, infection, and wound breakdown (Seruya et al., 2011). The reoperation rate was 10.8% and was correlated to syndromic diagnosis, bicoronal involvement, and age younger than 6 months. Goobie et al. examined

225 patients at Boston Children's Hospital between 2002 and 2012, assessing for post-operative hematological and cardiorespiratory complications requiring ICU admission (Goobie et al., 2015). The incidence of cardiorespiratory events was 14.7% and the incidence of hematological events was 29.7%; predictors of hematological events were body weight less than 10kg, ASA classification of 3 or 4, and blood transfusion greater than 60mL/kg (Goobie et al., 2015).

Earlier craniosynostosis repair surgeries from the 19th century had higher complication rates and poorer long-term outcomes, but this has been steadily improving over the years (Derderian and Seaward, 2012). Looking at outcomes, Alperovich et al. surveyed 53 surgeons about their craniosynostosis repair procedures, finding that 100% of them completed the repairs before age one and the majority between 4-8 months (Alperovic et al., 2015). The best outcomes occur for surgeons with over ten years of experience, and those surgeons also had shorter operative times (Alperovic et al., 2015). Among those surveyed, Intensive Care Unit (ICU) necessity was examined and only 4.7% of patients required ICU care and it was often those that had pre-existing end-organ dysfunction, high intraoperative blood loss, or syndromic cases (Alperovic et al., 2015). Attempts to reduce morbidity, hospital costs, and length of stay have been made at many institutions. With regard to length of stay (LOS), Lin et al. developed a clinical pathway intended to reduce ICU LOS for non-syndromic single suture CVR using comparative hospital data of ICU LOS, interventions, and perioperative morbidities including infection rate, cerebrospinal fluid leaks, and reoperations (Lin et al., 2019). They compared 51 patients using the new clinical pathway with 49 patients treated one year earlier and found a significantly shorter ICU LOS; patients were released 16 hours earlier on average (Lin et al., 2019). After CVR, patients are usually managed in the ICU but this has become less necessary due to overall reduction in perioperative complications which can be largely attributed to advances in anesthesia monitoring and blood transfusion protocols (Lin et al., 2019).The Agency for Healthcare Research describes Pediatric Quality Indicators (PDI) as accidental puncture or laceration rate, perioperative hemorrhage or hematoma rate, postoperative respiratory failure rate, postoperative sepsis rate,

and central venous catheter-related blood stream infection rate. These PDIs are used across several medical procedure evaluations to determine risk factors and their associated outcomes.

Reoperation rates have been used across several studies as an outcome measure for the quality of craniosynostosis repair. Pearson et al. performed a retrospective single-institution analysis of 20-year complication and reoperation rates of 494 patients accounting for diagnosis, sex, syndromic involvement, age, type of fixation, complications, and reoperation (Pearson et al., 2008). The study classified patients by metopic, unilateral coronal, bilateral coronal, sagittal, lambdoidal, and multiple-suture synostoses, finding that those with multiple, unilateral coronal, or bilateral coronal had the highest rates of major reoperation (Pearson et al., 2008). They defined major reoperations as repeat cranial reconstruction, osseous cranioplasty, bony debridement requiring bicoronal flap, or tissue expander placement for wound closure, and it was required in 38.1% of syndromic cases compared with only 19.5% of non-syndromic patients (Pearson et al., 2008). Morrison et al performed a retrospective analysis of open CVR by a single surgeon at New York Presbyterian Hospital from 1995 to 2015 where 81 patients were treated; 17.3% were syndromic and mean age was 13.8 months (Morrison et al., 2018). Mean length of stay was 4.31 days, mortality was 0%, rate of complications was 1.2%, and rate of reoperation was 2.5% over 20 years (Morrison et al., 2018). Limited studies have investigated postoperative readmissions and emergency department visits within 30 days of discharge from craniosynostosis repair. Wen et al. sampled 1120 patients and found that 8.8% had a hospital-based acute care encounter within 30 days (Xu et al., 2016). Of those, 56.6% were handled in the emergency department without readmission. African American and Hispanic patients were associated with more frequent encounters (Xu et al., 2016).

CVR is considered the historical gold standard for craniosynostosis repair, and the technique involves dissections and osteotomies that result in significant blood loss (Meier et al., 2016). Blood transfusion rates have been used universally as a quality measure for surgical procedures. A single center compared transfusion rates from 2004-2015 between experienced and less experienced neurosurgeons for 218 patients and found that overall transfusion rate was 24% with no difference with respect to surgeon

experience (Bonfield et al., 2016). Markiewicz et al. performed an assessment of the 2014 NSQIP sampling 756 patients, 503 of whom received transfusions, for whether blood transfusion in CVR is associated with increased LOS (Markiewicz et al., 2017). Blood transfusion was associated with increased LOS, 4.1 days compared to 3.0 days, but other contributing factors included race, ASA classification, premature birth, congenital malformations, and number of sutures involved (Markiewicz et al., 2017). A similar study by Chow et al. also utilized the NSQIP from 2012-2013 to determine risk factors for blood transfusion in CVR and the effects of transfusion on postoperative complications (Chow et al., 2015). Looking at 1059 patients, 73.4% required transfusion and 49.1% required more than 25mL/kg which is considered to be a safety threshold and quality measure (Chow et al., 2015). They recommend that current thresholds of 25mL/kg not be used as predictors of risk; a much higher threshold of 60mL/kg was shown to increase risk of complications and length of stay (Chow et al., 2015). Stricker et al. assessed practices in the management of craniofacial surgery, surveying 48 institutions for assessment of infants undergoing strip craniectomy and craniofacial reconstruction, concluding that transfusion thresholds should be developed (Stricker et al., 2011). Vanderbilt University compared craniofacial reconstructions of 41 patients from 2012, preceding their blood-sparing protocol, and 39 patients from 2013 after the initiation of the protocol (Nguyen et al., 2015). Employment of blood-sparing surgical techniques by the multidisciplinary team is associated with reduced intraoperative blood transfusions (Nguyen et al., 2015). Craniofacial reconstructions are associated with significant blood loss, and many protocols are in place to reduce rates of blood transfusion (Nguyen et al., 2015). Low blood transfusion rates are maintained by careful intraoperative technique and accepting lower hemoglobin levels in hemodynamically stable patients (Bonfield et al., 2016).

H. **Conclusion**

Craniosynostosis is a widely studied and understood condition with varying basis for diagnosis, risk factors, and treatment modalities. It can be concluded that syndromic patient populations require more acute and prudent care and management, as this group is higher risk for complications and poorer outcomes. Complications related to surgical procedures on such young patients are vast and carry significant

morbidity, which speaks to the importance of universal protocols to improve quality of care. Collaboration and multicenter trials would be beneficial to the determination of optimal practices due to the low incidence of craniosynostosis and low sample sizes at any one institution (Stricker et al., 2011).

III. MATERIALS AND METHODS

A. Database

The Nationwide Inpatient Sample (NIS) was utilized for the years 2012-2014. It is a stratified sample comprised of 20% of United States acute-care non-federal hospitals made to represent all hospitalizations nationwide ("Nationwide Inpatient Sample", 2019). The hospitals accounted for include information on hospital ownership, geographic location, bed count, and teaching status, as well as report data on all yearly hospitalizations. A discharge weight is given to each case of hospitalization and contributes to weighted national outcome estimates. The variables assessed are patient demographics, comorbidities, procedures, outcomes such as disposition, length of stay, and hospital charges. The Agency for Healthcare Research and Quality (AHRQ) sponsors the Healthcare Cost and Utilization Project (HCUP) which includes the NIS.

B. Data User Agreement and Institutional Review Board Approval

The data user agreement was signed with the HCUP-AHRQ before the study began. Cell counts less than or equal to 10, designated "DS" for discharge information suppressed, were not reported to maintain patient confidentiality per this agreement. This study was exempt from institutional review by the University of Illinois at Chicago College of Dentistry.

C. Case Selection

The patient cohort was selected using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure code per the protocol of Nguyen et al (2013). This code is inclusive of surgical procedures such as opening of the cranial suture (procedure code 02.01), formation or repair with a bone flap (02.03), skull bone graft or pericranial graft (02.04), or other osteoplasties (02.06) ("Classification of disease, functioning, and disability", 2019). Patients who were analyzed were under 3 years old and had both surgical repair and a diagnosis code in the NIS database.

D. Dependent Variables

The outcome variables of interest in this study are occurrence of complications, length of stay, and hospital charges.

E. Independent Variables

The independent variables included in this study are all patient- and hospital-level factors, including patient age, sex, race, household income, insurance status, comorbid conditions, hospital bed size, region, and teaching status.

F. Machine Learning Approach

Two Neural Network Models were developed to test our study hypothesis. In the first model, co-morbid burden was used as a continuous variable while in the second model the individual co-morbid conditions were used as the input variables. The Neural Network Models were developed using Multilayer Perception. The independent variables were used as in the in-put layer for both models. Number of hidden layers in models were specified by automatic architecture selection. Normalized importance was computed for each variable in the input layer. The dataset was partitioned into training (70%) and testing (30%) datasets. All statistical analyses were conducted using SPSS Version 25.0 software (IBM Corp, NY) (Allareddy et al., 2019).

IV. RESULTS

A. Descriptive Statistics

There were 8360 patients undergoing craniosynostosis repair analyzed in the NIS through 2012-2014. The mean age at admission was 0.4 years, and 75.3% of patients were under one year old, as seen in TABLE I. Approximately two-thirds of patients were male and one-third were female as described in TABLE II. The mean length of stay was 4.3 days and mean total hospital charges were $91,795. Hospital admission was elective for 7905 of patients, or 95% as described in TABLE III. 280 patients experienced an infectious complication for an overall infection rate of 3.35%. The types of infection are detailed in TABLE IV. Payers are outlined in TABLE V; private insurance paid for 4020 of the repair procedures while Medicaid covered 3635 patients. No comorbid conditions were reported in 6065 patients, with the remainder having one or more conditions as shown in TABLE VIA. Table VIB describes the frequencies of different comorbidities among patients. Deficiency anemias were found in 11.5%, chronic blood loss anemia in 0.96%, chronic pulmonary disease in 2.9%, and coagulopathy in 3.0%. Patients with hypertension comprised 0.96%, 0.24% had hypothyroidism, 0.06% had liver disease, 10.3% had fluid and electrolyte disorders, and 4.6% had other neurological disorders. There was 0.06% of patients with obesity, 0.41% with paralysis, 0.12% with peripheral vascular disorders, 0.24% with pulmonary circulation disorders, 0.12% with renal failure, 0.66% with valvular disease, and 0.24% with weight loss.

TABLE I
AGE IN YEARS AT ADMISSION (AGE)

Condition	Nationwide Estimate	Percent
0	6300	75.3%
1	1060	12.6%
2	745	8.9%
3	255	3.0%

TABLE II

INDICATOR OF SEX (SEX)

Condition	Nationwide Estimate	Percent
Male	5420	64.8%
Female	2940	35.1%

TABLE III

ELECTIVE VERSUS NON-ELECTIVE ADMISSION (ELECTIVE)

Condition	Nationwide Estimate	Percent
Elective	7905	94.6%
Non-Elective	455	5.4%

TABLE IV
INFECTION

Condition	Nationwide Estimate	Percent
Septicemia	20	0.23%
Bacterial	95	1.14%
Viral	100	1.20%
Mycoses	75	0.90%
Pneumonia	15	0.18%
Overall Infection	280	3.35%

TABLE V
PRIMARY EXPECTED PAYER (PAY1)

Condition	Nationwide Estimate	Percent
Medicare	15	0.2%
Medicaid	3635	43.6%
Private Insurance	4020	48.2%
Self Pay	80	1.0%
No Charge	DS	DS
Other	590	7.0%

TABLE VIA
NUMBER OF COMORBID CONDITIONS

Condition	Nationwide Estimate	Percent
0	6065	72.5%
1	1745	20.8%
2	395	4.7%
3	120	1.4%
4+	35	0.42%

TABLE VIB

TYPES OF COMORBID CONDITIONS

Condition	Nationwide Estimate	Percent
Deficiency Anemias	965	11.5%
Chronic Blood Loss Anemia	80	0.96%
Chronic Pulmonary Disease	240	2.9%
Coagulopathy	250	3.0%
Hypertension	80	0.96%
Hypothyroidism	20	0.24%
Liver Disease	DS	DS
Fluid and Electrolyte Disorders	860	10.3%
Other Neurological Disorders	385	4.6%
Obesity	DS	DS
Paralysis	35	0.41%
Peripheral Vascular Disorders	DS	DS
Pulmonary Circulation Disorders	20	0.24%
Renal Failure	DS	DS
Valvular Disease	55	0.66%
Weight Loss	20	0.24%

Hospital bed size categories vary by region in that small, medium, and large classifications encompass a different number of beds dependent on the hospital's location. In the Northeast region, rural hospitals are classified as small with 1-49 beds, medium with 50-99 beds, and large with over 100 beds. In Northeastern urban non-teaching hospitals, they are classified as small with 1-124 beds, medium with 125-199 beds, and large with over 200 beds. In Northeastern urban teaching hospitals, they are classified as

small with 1-249 beds, medium with 250-424 beds, and large with over 425 beds. The Midwestern rural hospitals are classified as small with 1-29 beds, medium with 30-49 beds, and large with greater than 50 beds. The Midwestern urban non-teaching hospitals are classified as small with 1-74 beds, medium with 75-174 beds, and large with over 175 beds. The Midwestern urban teaching hospitals are classified as small with 1-249 beds, medium with 250-374 beds, and large with greater than 375 beds. The Southern regional rural hospitals are classified as small with 1-39 beds, medium with 40-74 beds, and large with more than 75 beds. The Southern urban non-teaching hospitals are small with 1-99 beds, medium with 100-199 beds, and large with more than 200 beds. The Southern urban teaching hospitals are small with 1-249 beds, medium with 250-449 beds, and large with over 450 beds. Lastly, Western region rural hospitals are classified as small with 1-24 beds, medium with 25-44 beds, and large with greater than 45 beds. The Western urban non-teaching hospitals are small with 1-99 beds, medium with 100-174 beds, and large with over 175 beds. The Western urban teaching hospitals are classified as small with 1-199 beds, medium with 200-324 beds, and large with greater than 325 beds. The distribution of repair procedures by region and hospital bed size is described in TABLES VII and VIII. Locations and teaching status of the hospitals are listed in TABLES IX.

TABLE VII
BED SIZE OF HOSPITAL (HOSP_BEDSIZE)

Condition	Nationwide Estimate	Percent
Small	975	11.6%
Medium	2455	29.4%
Large	4930	59.0%

TABLE VIII
REGION OF HOSPITAL (H_REGION)

Condition	Nationwide Estimate	Percent
Northeast	1345	16.1%
Midwest or North Central	1805	21.6%
South	3190	38.2%
West	2020	24.2%

TABLE IX
LOCATION/TEACHING STATUS OF HOSPITAL (HOSP_LOCTEACH)

Condition	Nationwide Estimate	Percent
Rural	20	0.24%
Urban Non-teaching	105	1.26%
Urban Teaching	8235	98.5%

In the year 2012, 2785 craniosynostosis repair procedures were performed. 2755 cases were completed in 2013 and 2820 in 2014, as outlined in TABLE X. TABLE XI shows the distribution of patient race where 4500 were White, 1565 were Hispanic, 600 were Black, 150 were Asian or Pacific Islander, 70 were Native American, and 510 were categorized as other. Median household income was divided by quartiles and is listed in TABLE XII. There were 8165 patients discharged routinely, 155 discharged to home health care, 20 to another facility, and 15 to short-term hospitals as seen in TABLE XIII. TABLE XIVA shows the mean hospital charges as $86,490 and mean length of stay as 3.8 days for patients without infection, while charges were averaged at $244,384 and length of stay at 18.9 days for patients with infection. Similarly, TABLE XIVB depicts comorbid burden and the associated increase in infection rate,

hospital charges, and length of stay. TABLES XV, XVI, and XVII show the infection rates of race, admission type, and age, respectively.

TABLE X
CALENDAR YEAR (YEAR)

Condition	Nationwide Estimate	Percent
2012	2785	33.3%
2013	2755	33.0%
2014	2820	33.7%

TABLE XI
RACE (RACE)

Condition	Nationwide Estimate	Percent
White	4500	60.1%
Black	600	8.1%
Hispanic	1565	21.2%
Asian or Pacific Islander	150	2.0%
Native American	70	0.9%
Other	510	6.9%

TABLE XII
MEDIAN HOUSEHOLD INCOME NATIONAL QUARTILES FROM 2014 FOR PATIENT ZIP CODE (ZIPINC_QRTL)

Condition	Nationwide Estimate	Percent
$1-39,000	2010	24.4%
$40,000-50,999	2105	25.5%
$51,000-65,999	2220	26.9%
$66,000+	1910	23.2%

TABLE XIII
DISPOSITION OF PATIENT AT DISCHARGE (DISP)

Condition	Nationwide Estimate	Percent
Routine	8165	97.7%
Short-Term Hospital	15	0.12%
Another Type of Facility	20	0.24%
Home Health Care (HHC)	155	1.85%
Died	DS	DS

TABLE XIVA
MEAN HOSPITAL CHARGES AND LENGTH OF STAY

Condition	Without Infection	With Infection
Hospital Charges (in $)	86490	244384
Length of Stay (in days)	3.8	18.9

TABLE XIVB

COMORBID BURDEN AND RATE OF INFECTION, HOSPITAL CHARGES, AND LENGTH OF STAY

Comorbid Burden	Infection Rate	Hospital Charges in $	Length of Stay in Hospital in Days
0 (no comorbid conditions)	1.9%	$78,536	3.4
1	6.3%	$118,785	5.9
2	7.6%	$133,524	7.3
3	12.5%	$168,094	10.4

TABLE XV

RACE AND RATE OF INFECTION

Race	Infection Rate
White	2.8%
Black	4.2%
Hispanic	3.5%
Asian or Pacific Islander	13.3%
Native American	-
Others	2.9%
Missing Info on Race	4.1%

TABLE XVI

TYPE OF ADMISSION AND RATE OF INFECTION

Type of Admission	Infection Rate
Emergency/Urgent	16.5%
Elective	2.6%

TABLE XVII
AGE AND RATE OF INFECTION

Age (in years)	Infection Rate
Less than 1 year	2.9%
1	5.2%
2	4%
3	3.9%

B. **Machine Learning Models**

The Machine Learning analytical method delivered numerous results where the dependent variable was the occurrence of infection. TABLE XVIII summarizes the training and testing case load for both models. Model #1 had 3.8% incorrect predictions and an accuracy of 96.2%, while Model #2 had 3.7% incorrect predictions and an accuracy of 96.3% in the testing samples. TABLE XIX and Figure 1 depicts the normalized importance of all independent variables on the occurrence of infection. Figure 2 reports the accuracy of Model #1 in a receiver operating characteristic, plotting true positive against false positives with a resulting area of 0.828 under the curve. TABLE XX and Figure 3 depict the normalized importance of all individual comorbid conditions as independent variables on the occurrence of infection. AHRQ Comorbidities are defined by the Agency for Health Research and Quality ("Quality Indicators", 2019). Figure 4 reports the accuracy of Model #2 in a receiver operating characteristic, plotting true positive against false positives with a resulting area of 0.815 under the curve.

TABLE XVIII
CASE PROCESSING SUMMARY

Condition	Sample Size	Percentage
Training - Model #1	1034	71%
Testing - Model #1	422	29%
Training - Model #2	1021	70%
Testing - Model #2	435	30%
Total	1672	100%

TABLE XIX
NORMALIZED IMPORTANCE OF VARIABLES ASSOCIATED WITH OCCURRENCE OF INFECTION - MODEL #1

Condition	Normalized Importance
Presence of comorbidities	100.0%
Race	80.6%
Elective vs. non-elective	75.5%
Age 1-2	38.5%
Female	37.4%
Median household income	36.2%
Age 3+	27.2%
Region of hospital	26.8%
Age <1	24.9%
Type of craniotomy	24.6%
Private insurance	18.1%
Age 2-3	13.3%
Large hospital size	12.2%

Figure 1. Normalized Importance of Variables Associated with Occurrence of Infection - Model #1

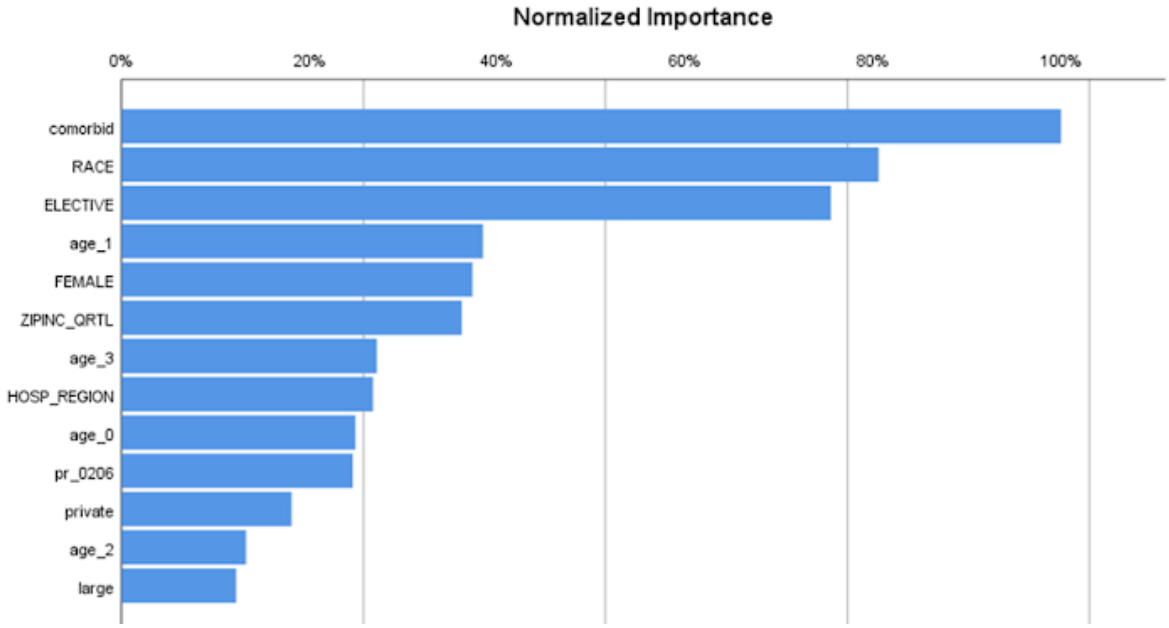


Figure 2. Probability of Detection versus Probability of False Alarm for Model #1

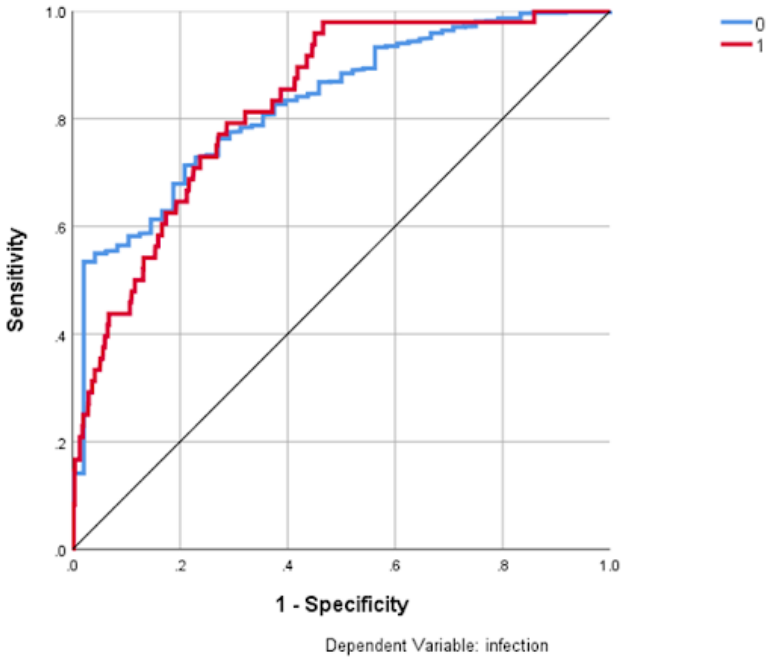


TABLE XX
NORMALIZED IMPORTANCE OF INDIVIDUAL COMORBID CONDITIONS ASSOCIATED WITH OCCURRENCE OF INFECTION - MODEL #2

Condition	Normalized Importance
Elective vs. non-elective	100.0%
Race	76.6%
Age 2-3	69.6%
AHRQ Comorbidity: other neurological disorders	69.0%
AHRQ Comorbidity: fluid and electrolyte disorders	59.6%
AHRQ Comorbidity: hypothyroidism	56.6%
AHRQ Comorbidity: chronic pulmonary disease	46.6%
AHRQ Comorbidity: weight loss	38.6%
Type of craniotomy	37.8%
Region of hospital	37.6%
AHRQ Comorbidity: blood loss anemia	36.4%
Female	33.9%
Private Insurance	27.1%
AHRQ Comorbidity: deficiency anemias	27.1%
AHRQ Comorbidity: pulmonary circulation disorders	26.2%
Large hospital size	23.4%
AHRQ Comorbidity: renal failure	22.5%
AHRQ Comorbidity: obesity	20.4%
Age 3+	19.5%
Median household income	18.8%
Age 1-2	17.2%
AHRQ Comorbidity: paralysis	12.9%
AHRQ Comorbidity: valvular disease	11.1%
Age <1	10.3%
AHRQ Comorbidity: coagulopathy	10.3%
AHRQ Comorbidity: hypertension	9.5%
AHRQ Comorbidity: peripheral vascular disorders	9.2%

Figure 3. Normalized Importance of Individual Comorbid Conditions Associated with Occurrence of Infection - Model #2

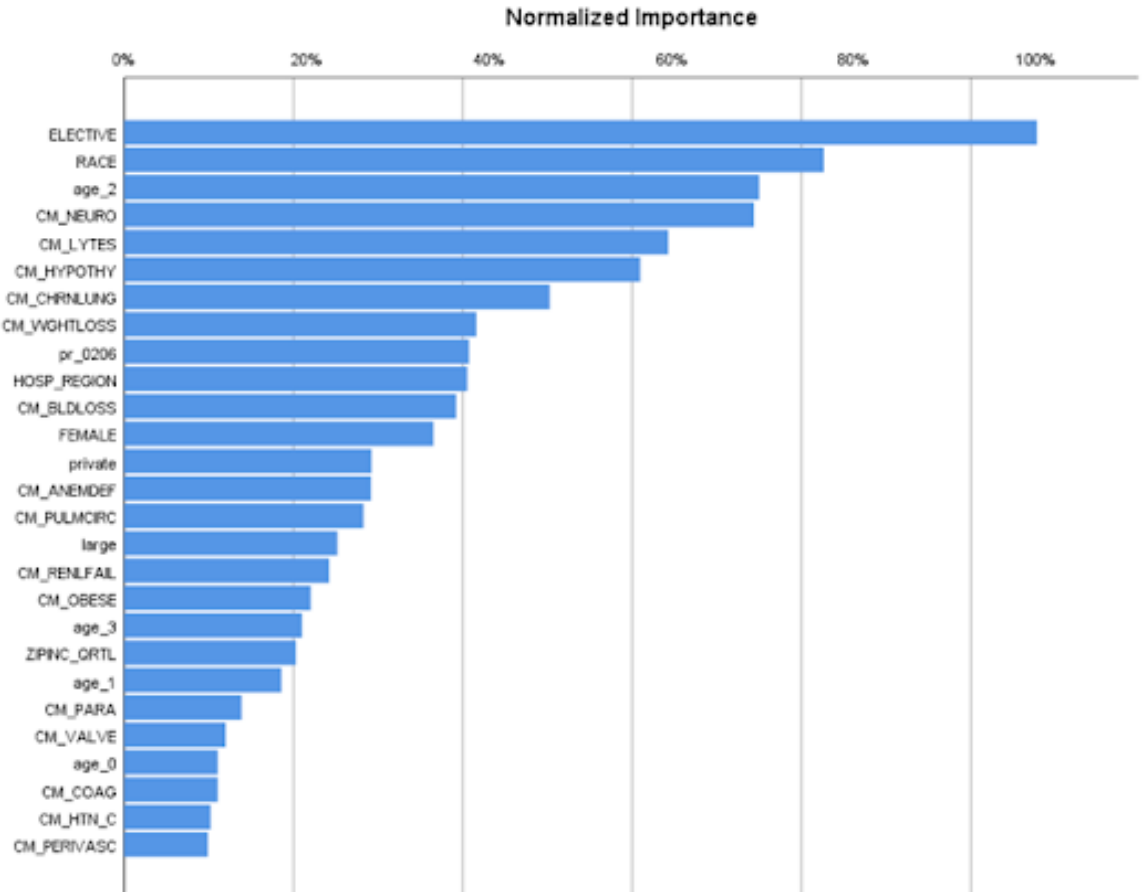
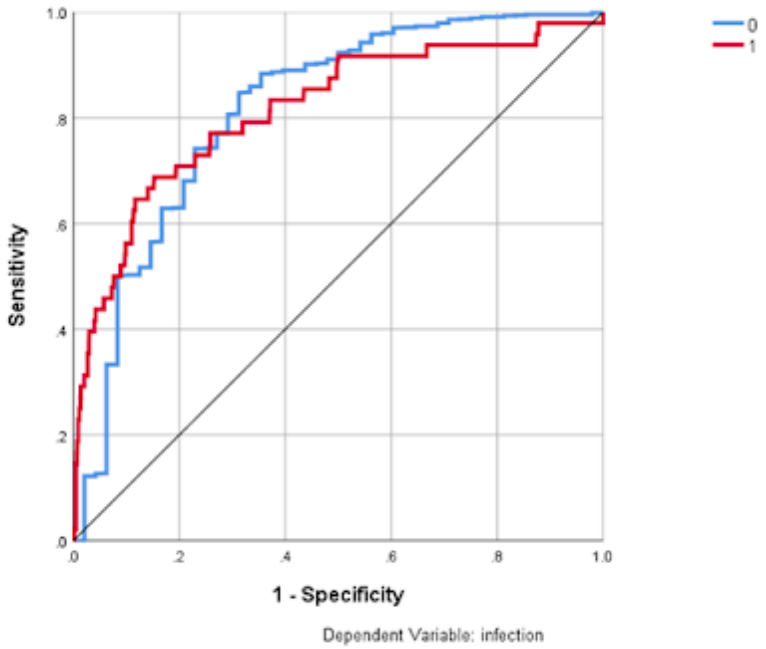


Figure 4. Probability of Detection versus Probability of False Alarm for Model #2



V. DISCUSSION

A. Comparison with the Literature

Patients in the study had a mean age at admission of 4.8 months old, and the vast majority (75.3%) were under one year old. This is younger than other studies that report private insurance patients' mean age at 6.8 months and Medicaid patients' mean age at 9.1 months old (Lin et al., 2015). Consistent with the Kids Inpatient Database study a decade earlier, the majority of cases included in our dataset are insured White males (Nguyen et al., 2013). Unlike previously reported data, our study accounts for income to include an equal number of patients for each quartile as seen in TABLE XII. Our study also shows an equal number of patients undergoing the procedure from 2012, 2013, and 2014. Hospital-related factors are shown to be highly relevant to outcomes per previous studies. Bed size and region are interrelated and categorized differently by region, but the overall majority of patients are admitted to large urban teaching hospitals. This is consistent with NIS data prior to 2010 that showed an increase in regionalization to major teaching hospitals (Allareddy, 2016). As noted by previous research, higher volume centers have lower odds of complications as well as decreased cost and length of stay (Wu et al., 2018). Complication rate in this study was determined to be 3.3%, equal to several other studies that report a range of 3.3-3.6% (Jeong et al., 2013).

The number of comorbidities showed the highest correlation to adverse outcomes in patients undergoing repair procedures. Of those, neurological disorders, fluid and electrolyte disorders, and hypothyroid were the strongest indicators of complication. Our data reported that 72.5% of patients did not have any comorbidities, but that 20.8% had one, 4.7% had two, and 1.4% had three comorbidities. Per previous research, increased comorbid burden is associated with higher rates of complication and therefore longer length of stay and increased hospital costs (Prakasam et al., 2018) (Lam et al., 2016). Longer length of stay has been shown to double hospital costs (Nguyen et al., 2013). No previous studies have discerned the importance of different comorbidities in combination with other factors to determine association with

infectious complications. This is a novel approach made possible with the use of machine learning as an analytical model.

In terms of individually analyzed factors, of secondary and tertiary relevance are race and elective procedure. At a normalized importance of 80.6%, being non-White is strongly correlated with development of an infectious complication. Previous studies report data that patients who are African American or Hispanic have more frequent acute-care encounters within 30 days of discharge (Xu et al., 2016) and that non-White patients have a later time of operation by approximately two months (Lin et al., 2015). Therefore it can be extrapolated that non-white patients would have an increased risk of infectious complication, but no data has been reported specifically on the association of complication rates and race. Recall that non-white patients are also less likely to be treated at high-volume hospitals, which has shown correlation with increased risk of infection as well (Chattha et al., 2018). Additionally, elective versus non-elective procedure correlation with the occurrence of complications has not been precisely presented in other research, but this study found a strong association with the need for non-elective surgical intervention and the development of infection. With a normalized importance of 75.5%, it can be stated that patients requiring non-elective surgery are at a far higher risk of negative outcomes.

Patient age and sex are of significance, with patients undergoing surgical repair between age one and two having a normalized importance of 38.5% and being female having a normalized importance of 37.4% in Model #1. That being said, patients under one year of age, between two and three, and over three have normalized importance of 24.9%, 13.3%, and 27.2%, respectively. It can be deduced that the highest risk of complication is associated with an age between one and two at the time of operation when using Model #1, but this does not account for differentiation between comorbidities. When compared with the literature, it has often been stated that surgical repair before one year of age is optimal (Bruce et al., 2018), but there is no reported evidence on the infectious complication risk for each year of life older than age one. This study demonstrates that the highest risk for complication occurs between one and two years of age, and therefore it can be inferred that if surgical repair cannot be completed by one year old, the procedure

should not be completed until the patient is over two years old. Median income in this study was described as having a normalized importance of 36.2%, where other studies have also shown a correlation between income and insurance status and earlier time of surgery (Lin et al., 2015). It is expected that patients of a higher socioeconomic status will have earlier access to care and therefore more favorable outcomes with respect to infectious complications, as well as private insurance. However, cofactors of less importance are hospital region, type of craniotomy, private versus Medicaid insurance, and large hospital size.

When differentiating for types of comorbidities as defined by the Agency for Healthcare Research and Quality, Model #2 displays elective procedure, race, age, and comorbidities as the highest predictors, similar to Model #1. The distinction lies in the specific comorbid condition, with neurological disorders, fluid and electrolyte disorders, and hypothyroidism showing the strongest normalized importance. Following those are chronic pulmonary disease and weight loss. Other studies have neglected to differentiate between these specific comorbidities and their association with the occurrence of infectious complications. There have been reports in the literature of overall comorbid burden having a correlation with poor outcomes and increased odds of developing an infection (Prakasam et al., 2016). Studies have also shown that comorbid burden is associated with increased length of stay, specifically in patients between ages one and three (Nguyen et al., 2013). The discrepancy in importance between Models #1 and #2 can be explained by the analysis of overall comorbid burden in Model #1, as opposed to a distinction between each comorbid condition depicted in Model #2. For the sake of thoroughness, both models were included in the study. However, Model #2 is more clinically significant in that each condition with higher contribution to the development of infection can be identified in high-risk patients. Each hospital can then develop its own protocol to optimize quality of care and reduce the risk of infectious complication and resultant costs and length of stay on an individual basis.

Overall, the most significant outcome of this project is its profound depiction of the burden of patients experiencing an infectious complication on the healthcare system. These high-risk patients are expected to have a length of stay 6x higher at 18.9 days and a hospitalization charge almost 3x higher at an

average of $244,385. Furthermore, the number of comorbidities shows a positive linear association with infection rate, hospital charges, and LOS. As infection is considered a never-event in craniosynostosis repair surgeries, it is imperative that high-risk patients are identified early and proper precautions are implemented to ensure positive outcomes pre-, peri-, and post-operatively. Based on all collected data and subsequent analyses in this study, it can be stated that the patient most likely to develop an infectious complication is a non-White infant between the ages of one and two, insured under Medicaid, having a non-elective or emergency procedure, with more than one comorbidity, the worst of which would be neurological disorders, fluid and electrolyte disorders, or hypothyroidism.

B. **A Novel Machine Learning Approach**

The Deep Neural Network used two models in this study to analyze the importance of the hospital- and patient- level factors and their association with the development of infectious complications. This approach is novel in that previous linear regression analyses were unable to account for the infinite combination of factors and their resultant outcomes. The deep neural network, or machine learning component, uses a large fraction of the dataset to develop its own algorithms and "learn" how to accurately analyze a second subset, called the testing set (Allareddy et al., 2019). Both models predicted outcomes across the multitude of factor combinations with extremely high accuracy of over 96%; this broad scope and robust output is inherently lacking in traditional linear regression analyses.

C. **Limitations**

Limitations of the study encompass those usually attributed to the use of a secondary dataset. These analyses are inherently limited in that this is a retrospective cohort and no causation can be attributed to the variables and outcomes. It would be most valuable in the future for prospective longitudinal studies to attempt to determine a cause-and-effect relationship between the patient- and hospital-level factors and poor surgical outcomes. The NIS database itself limits variables available for analysis, including age, race, gender, and comorbidities, but does not account for confounding variables such as differences in hospital-

specific protocols. It is also notable that there is only one code available for craniosynostosis in the ICD-9-CM despite variation in type of suture, severity, and number of affected sutures, which does not allow for differentiation within this variable and cannot be adjusted for. Furthermore, the dataset does not include information on post-discharge outcomes and these long-term effects on health were not assessed. Lastly, it should be stated that the hospital charges outcome variable encompasses only the procedural amount charged to the patient and excludes other indirectly associated costs such as anesthesia fees, surgeon fees, medications, or specialist consultation fees. True costs are estimated to be higher than those reported in this study.

VI. CONCLUSION

We developed a novel neural network model to accurately classify those who were highly likely to develop infections, have longer length of stay in hospital, and have high hospitalization charges amongst those undergoing craniosynostosis repairs. High-risk patients can be identified and managed to reduce the profound burden on the healthcare system.

APPENDIX A

Notice of Determination of Human Subject Research

October 31, 2018

20181289-118038-1

Shayna Azoulay-Avinoam
Orthodontics

RE: **Protocol # 2018-1289**
Model Machine Learning Approaches to Examine Surgical Outcomes in Patients with Craniosynostosis

Sponsor:	American Association of Orthodontists Foundation
PAF#:	Not available
Grant/Contract No:	Not available
Grant/Contract Title:	Not available

Dear Azoulay-Avinoam:

The UIC Office for the Protection of Research Subjects received your "Determination of Whether an Activity Represents Human Subjects Research" application, and has determined that this activity **DOES NOT meet the definition of human subject research** as defined by 45 CFR 46.102(f).

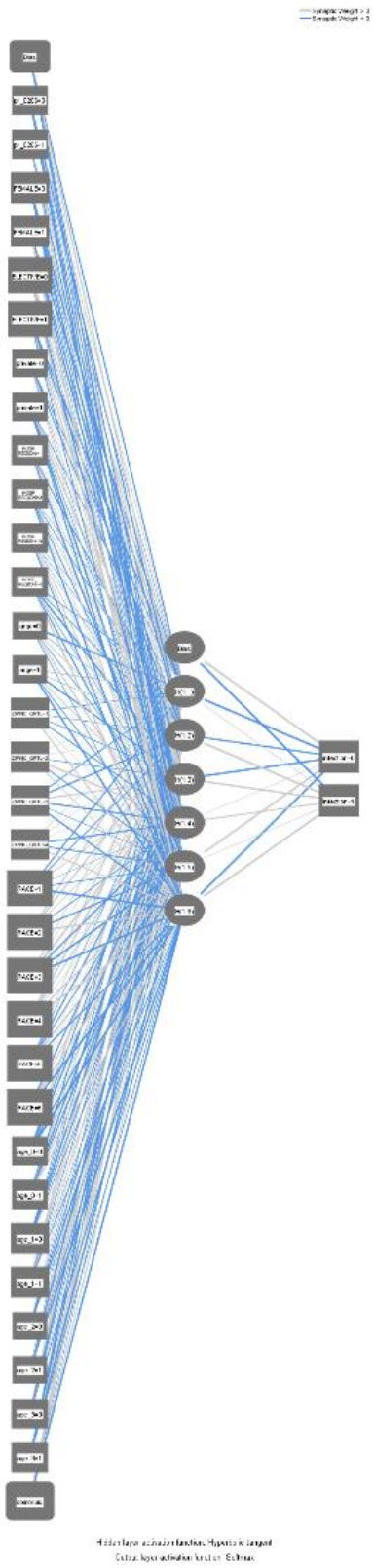
Specifically, the Nationwide Inpatient Sample for the years 2000 to 2018 will be used for the proposed study. The Nationwide Inpatient Sample is a publicly available, de-identified data set. Data will be analyzed using statistical tests and novel machine learning approaches to discern patterns in surgical outcomes and to build predictive models. As such, there will be no interactions or interventions with individuals, nor will there be any use of private, identifiable information.

You may conduct your activity without further submission to the IRB.

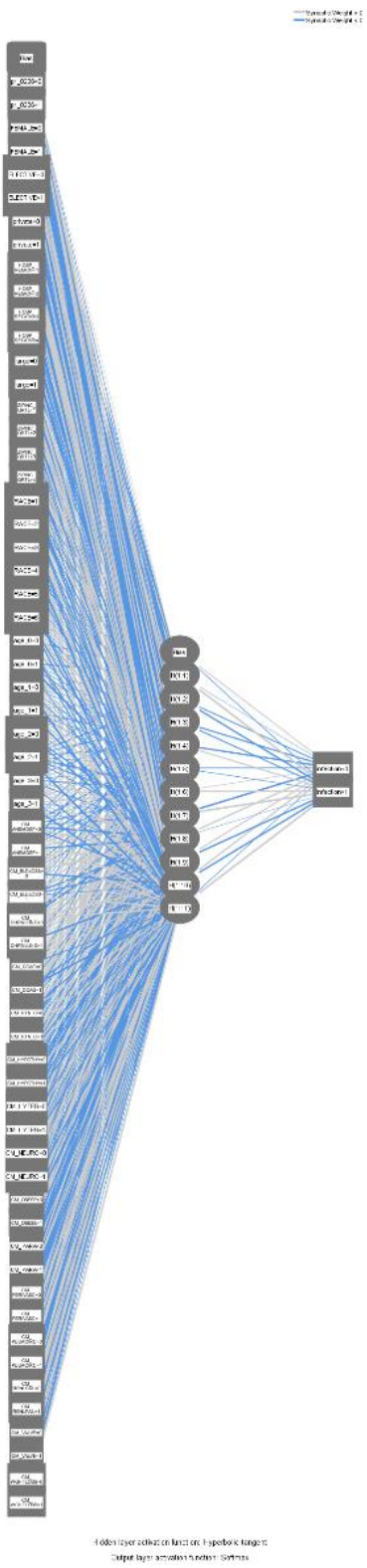
If this activity is used in conjunction with any other research involving human subjects or if it is modified in any way, it must be re-reviewed by OPRS staff.

UNIVERSITY OF ILLINOIS AT CHICAGO
Office for the Protection of Research Subjects
201 AOB (MC 672)
1737 West Polk Street
Chicago, Illinois 60612
Phone (312) 996-1711

APPENDIX B



APPENDIX B (Continued)



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