# ABSTRACTS

# Medical Student Research Conference September 12 – 14, 2018

University of Iowa Roy J. & Lucille A. Carver College of Medicine

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# Hip Wire Navigation Decision Making

Roshan Abid, Steven Long, Geb Thomas, Matthew Karam, Donald D. Anderson **Disclosures**: Roshan Abid (N), Steven Long (Iowa Simulation Solutions, LLC), Geb Thomas (Iowa Simulation Solutions, LLC), Matthew Karam (Iowa Simulation Solutions, LLC), Donald D. Anderson (Iowa Simulation Solutions, LLC)

INTRODUCTION: Becoming a board-certified orthopaedic surgeon in the United States requires the successful completion of a surgical residency, standardized tests, review of sample cases, and evaluation of surgical logs, but does not require a formal surgical competency. Moving toward a system more focused on resident competency requires the establishment of performance metrics that can be reliably evaluated and clearly indicate surgical ability. Wire navigation is a core skill in orthopaedics that involves the interpretation of 2-D fluoroscopic images to place a guide wire through a specified path in bone. In intertrochanteric fracture cases, the tip-apex distance (TAD), a measure of the guide wire placement in bone, has often been used as a performance metric for assessing a surgeon's wire navigation skills, because larger TADs are highly correlated with failure outcomes. However, the TAD misses much of the actual wire navigation process, as it is only calculated from the final positioning of the K-wire. In the wire navigation process, the surgeon makes a number of wire adjustment decisions based on each fluoroscopic image. In this study, data taken from simulated wire navigation decision-making analysis. The objectives of this study are to (1) evaluate resident performance on simulated and actual hip wire navigation tasks using multiple potential performance metrics and (2) establish relationships between performances in these two environments.

METHODS: This study analyzed wire navigation performance on a simulator and in the operating room (OR). Simulator data was collected as part of a study examining the effects of practicing wire navigation on an augmented reality simulator (Iowa Simulation Solutions, LLC). Sixty-four first-year orthopaedic residents from the University of Iowa (12), the University of Minnesota (24), the Mayo Clinic (23), and the University of Nebraska (5) participated in the study. Residents were given 30 minutes to practice placing a guide wire on the augmented reality simulator, which provided computer generated AP and lateral pseudo-fluoroscopic images as a Kwire was drilled into a Sawbones proximal femur. The simulator detects the wire position relative to the Sawbones femur each time a resident requests a new guiding fluoroscopic image, providing a unique history of the task. In the OR, intra-operative fluoroscopic images were saved during sixteen intertrochanteric fracture cases, in which residents placed K-wires before placing a sliding hip screw. The fluoroscopic images were then used to locate position coordinates of the wire tip, the wire entry point, and the apex of the femoral head. The apex was identified using the methodology presented by Johnson et al<sup>1</sup>. The slope between the wire tip and wire entry point represented the trajectory of the wire, while the slope between the wire entry point and the apex represented the ideal wire trajectory, because this trajectory minimizes the TAD. These two datasets for the simulator and OR environment were then used to evaluate decisions made between each fluoroscopic image during the procedure. Decision-making was analyzed by comparing the change in wire angle between consecutive fluoroscopic images with the angular change needed to minimize the TAD. For example, if the resident made an adjustment that worsened their trajectory (i.e., moved it away from one that minimized the TAD), that was counted as an incorrect decision. Other decision analyses included examining if a resident switched between AP and lateral imaging views at appropriate instances, and also if they advanced the K-wire into bone at appropriate instances. Correct decisions made at these key points were summed over the procedure and compared to other metrics such as the number of fluoroscopic images used, the TAD, and a surgeon's experience level (based on the number of sliding hip screw cases performed).

RESULTS: On average, residents made 4 incorrect decisions on the simulator, whereas they made 9 in the OR. Residents averaged 13 correct decisions on the simulator and 23 in the OR. For the simulator, there was a strong positive correlation ( $R^2 = 0.57$ ) between the number of incorrect decisions and the number of images requested by residents. In the OR, a similarly strong positive correlation ( $R^2 = 0.76$ ) was found between incorrect decisions and number of images used. In both the simulated environment and the OR, a weak correlation was found between the number of incorrect decisions and the final TAD ( $R^2 = 0.10$  and  $R^2 = 0.06$ , respectively). In the OR, surgeon experience level had a moderate correlation ( $R^2 = 0.21$ ) with the number of incorrect decisions.

DISCUSSION: This study offers a unique insight into each step of the wire navigation procedure. Although two residents can theoretically achieve the same TAD value, one could have made more incorrect decisions in the process. This information is valuable when training residents. It would be beneficial to clearly demonstrate to a resident the key points in a procedure when a poor decision was made that might have led to additional fluoroscopic images being taken, and thus additional radiation exposure to a patient, to correct a mistake. This analysis can also identify residents' erroneous tendencies or quirks to individualize competency training. Furthermore, these new measurements have similar relationships in the simulated environment and OR. A major aspect of providing applicable training on a simulator is establishing that performance on a simulator correlates to performance in the OR. Although the residents that participated in the simulator were not the same residents that performed in the OR, this study begins to establish a link that wire navigation decision-making on a simulator is related to wire navigation decision-making in the OR.

SIGNIFICANCE/CLINICAL RELEVANCE: Measuring surgical decision-making has both potential training benefits as well as benefits to patients. By reducing surgical decision-making errors, surgeons may reduce the number of fluoroscopic images requested, decreasing the radiation exposure to patients and potentially producing better outcomes in wire navigation procedures.

**Title:** Positive feedback between PI3K $\delta$  and glucocorticoids sensitizes resistant B-cell Precursor Acute Lymphoblastic Leukemia cells to treatment

# Authors: Ossama Abu-Halawa, Mimi Fang, Ryan Mahling, Karina Kruth, and Miles Pufall

**Abstract:** We are interested in how the glucocorticoid receptor (GR), a steroid-activated transcription factor, integrates signals to direct B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL) cell death. This is of particular importance to resistant patients, some 10%-20% of children with BCP-ALL, whose treatment failure is closely linked to response to one component of their chemotherapy: glucocorticoids (GCs). To this day, survival is accurately predicted by response of leukemic blasts to GCs.

Our initial focus is on PI3K $\delta$ , a component of the growth and survival B cell receptor pathway. We recently showed superadditivity between PI3K $\delta$  inhibition by a small molecule inhibitor, CAL-101, and the GC dexamethasone (dex) in inducing cell death. We hypothesize that CAL-101 potentiates GC-induced cell death by enhancing dex induced gene regulation of key genes. We assayed the regulation of key genes in three BCP-ALL cell lines, NALM-6, RCH-ACV, and SUP-B15, each of which has a different degree of GC and PI3K $\delta$  sensitivity. To do this, we used quantitative real-time PCR (qPCR) to measure the effect of CAL-101 on GC-driven expression of key genes involved in GC-induced cell death, which we term causative genes.

We found that inhibition of PI3K $\delta$  enhanced dex regulation of most genes. In some cases, this appeared to be working directly through GR, in others by co-regulating the genes. We also discovered that regulation of all causative genes is not required for cell death, suggesting a cell-type specific program exists in different genetic backgrounds. Specifically, we found that CAL-101 (PI3K $\delta$  inhibition) potentiates GC gene regulation in a gene and cell specific manner. GCs repress PI3K $\delta$  expression, and PI3K $\delta$  activity represses GC causative gene regulation, forming a positive feedback loop. The synergistic relationship established between PI3K $\delta$  inhibition and dex suggest a promising, rational, combination chemotherapy patients with for treatment refractory BCP-ALL.

# The Effect of Monoamine Reuptake Inhibitors in Seizure Susceptibility on DBA/1 Mice

Hassan A. Ahamed, YuJaung Kim, Eduardo Bravo, and George B. Richerson

Department of Neurology, Department of Biomedical Engineering, Department of Molecular Physiology and Biophysics, The VA Medical Center

### Introduction

DBA/1 mice suffer from audiogenic seizures that lead to seizure-induced respiratory arrest (S-IRA) and death. It has been previously shown that the selective serotonin reuptake inhibitor (SSRI) fluoxetine can stop these mice from having tonic-clonic seizures and protect them from S-IRA. In the current study, the effect of fluoxetine, escitalopram, and milnacipran were investigated. Since fluoxetine is known to have various off-target effects, including norepinephrine reuptake inhibition, escitalopram was employed as a more selective SSRI. Milnacipran was used as an agent almost equally selective to serotonin and norepinephrine.

# Methods

At postnatal day 21 - 24 DBA/1 mice were primed in order to have 100% seizure susceptibility, this included 3 - 5 days of seizure induction using an audiogenic stimulus. After priming, the mice were injected with a dose of a drug and tested for seizures, 30 minutes after injection. If the mice had a severe seizure that resulted in S-IRA, they were resuscitated and re-used again one week later, after the drug had cleared from their system. If the mice did not have S-IRA, they were still used one week later at a different dose of the drug chosen.

# Results

At 100 mg/kg of fluoxetine, DBA/1 mice were completely protected from audiogenic seizures (n = 6 of 6). All other doses of fluoxetine were ineffective at protecting the mice from seizures and S-IRA expect one account at 1 mg/kg (n = 29 of 30). At 100 mg/kg, escitalopram completely protected some mice (n = 2 of 6), stopped tonic-clonic seizures (n = 1 of 6), and had no protective effect on tonic-clonic seizures + S-IRA (n = 3 of 6). At lower doses, escitalopram was completely ineffective at stopping seizures and S-IRA (n = 30 of 30). At 100 mg/kg of milnacipran, mice died (n = 4 of 6) before stimulation. One mouse was protected completely from seizures + S-IRA (n = 1 of 6) and one was not protected from seizures and S-IRA (n = 1 of 6). One account at 30 mg/kg protected from tonic-clonic seizures + S-IRA (n = 1 of 6) and another at 10 mg/kg (n = 1 of 6). All other doses were ineffective at protecting from seizures and S-IRA (n = 28 of 30).

# **Conclusions/Discussion**

DBA/1 mice were effectively protected from seizures and S-IRA using escitalopram and fluoxetine, but milnacipran did not show significant protective properties. In the future, we'd like to better understand why some drugs in the monoamine reuptake class work well at protecting DBA/1 mice from seizures and others do not. We'd also like to apply this model to a more chronic dosing scheme, more reminiscent to how human patients are treated therapeutically.

#### Improving Rotamer Optimization Using an X-ray Target Function

Soham Ali, Andrew Thiel, Jacob Litman, Mallory Tollefson, Michael Schnieders

#### Introduction

Non-covalent binding of molecules forms the basis of innumerable biological processes such as hormone-receptor binding, antigen-antibody binding, and various stages of signaling cascades. Their widespread involvement and incredible specificity make them attractive targets for biomedical therapies. Tools to improve understanding of these intermolecular interactions would be useful in designing more effective therapeutics. Various imaging techniques, such as X-ray crystallography, have made numerous advancements in understanding protein structure. Refinement of these structures using computational tools such as Force Field X (FFX) has pushed these achievements further. The quality of the structures output by refinement is assessed by measuring their agreement with the original X-ray data, a value known as R<sub>free</sub>.

An important aspect of protein structure refinement is the determination of energetically favorable side-chain conformations called rotamers. Various libraries of identified rotamers for each amino acid have been defined in literature. Thus far however, refinement methods using these libraries have utilized the real-space coordinates obtained from a Fourier transform of the X-ray crystallography scattering data. These calculated data require additional information from the initial structure being refined, which biases the entire refinement procedure towards the original protein conformation. Improvements to FFX have enabled the use of original coordinates X-ray scattering data for refinement, eliminating the need for data from the original structure. In this paper, seven different PCNA structures previously refined using real-space coordinates are refined using X-ray coordinates, and the R<sub>free</sub> values of these structures is measured.

#### Purpose

- Does the improved refinement procedure yield improved R<sub>free</sub> scores?
- Does the refinement procedure yield more energetically favorable structures?

#### Methods

Each structure is first run through an initial refinement that aims to minimize the energy of the overall protein structure. Using the Richardson and Ponder library, potential rotamers for each amino acid are tested. The energetic favorability of each rotamer (self-energy) and its interactions with neighboring amino acids (two-body energy) is assessed, and the most optimal rotamers are selected. This is followed by a final minimization to optimize the overall protein again. The R<sub>free</sub> values were recorded after this step, and each structure's energy decrease throughout the refinement process was also recorded. Additionally, the final structures were validated by online structure validation tool, Molprobity, to assess the number of unfavorable rotamers.

#### Results

The R<sub>free</sub> values of each of the 7 structures was measured and compared to those obtained by the real-space refinement. The average R<sub>free</sub> obtained by realspace was 26.70, which was decreased to 26.44 using X-ray coordinates. The average energy change was decreased from -300 kJ/mol to -370 kJ/mol. The average percentage of unfavorable rotamers however, increased from 1.67 to 5.95%.

#### Discussion

While both average R<sub>free</sub> and the overall energy decreased modestly, values for many of the structures were improved significantly. However, further improvements could be achieved by incorporating three-body energies into the procedure, potentially allowing for selection of rotamers that improve the overall energy of the protein, and its agreement with X-ray scattering data. Future experiments will aim to make these changes. Additionally, generating a more thorough rotamer library or adjusting optimization parameters could be explored as methods to reduce unfavorable rotamers.

Title: Resident perceptions of cross-specialty interaction

Student: Christoffer Amdahl, M2 Mentors: Dr. Manish Suneja, MD, Dr. Muneera Kapadia, MD

**Background:** Resident physicians from both general surgery and internal medicine undergo comprehensive training that allows them to become self-sufficient practitioners. However, there is no formal literature regarding how residents' perception of communication with other specialties influences the way residents interact with one another and perceive conflict in the clinical setting. Conflict in healthcare can take many different shapes, and identifying any such barriers will enable graduate medical educators to implement a more formalized interdisciplinary communication skills curriculum for medical residents.

**Purpose:** This study will use mixed methods to investigate the perceptions that general surgery and internal medicine residents have about each other with regards to communication, and whether there are similarities in perceived conflicts and communication barriers between the two groups. We will investigate the relationship between the communication styles and perceptions of general surgery residents and internal medicine residents, and whether these contribute lead to conflicts in the workplace.

**Methods:** A multi-method approach including open-ended questions and Likert-type individual survey questions was administered to internal medicine and general surgery residents exploring their perceptions on their respective experiences with residents from the other specialty. Qualitative analysis identified key themes in residents' experiences interacting with their inter-departmental colleagues in regard to the behavioral trends and experiences gathered from the focus groups and surveys.

**Results**: Discussion of these interactions highlighted that resident physicians demonstrate the behaviors that either lend their support and understanding of residents' need for a collegial relationship between departments or imply a lack of support or understanding. Three major themes that contributed to the ease or difficulty in the resident interdepartmental interactions included explicit communication of expectations, program organizational structure, and the type of communication utilized between residents.

**Conclusions**: Resident physicians' perceptions of their colleagues from different specialties will have a significant impact on residency program culture and experience. The trends identified in this study may help to address the challenges that residents perceive from interacting with one another and prevent any such negative perceptions early in medical careers. Administration and faculty can also benefit by introducing educational experiences and communication skill workshops specifically designed at migrating such negative perceptions before they cause conflict in the workplace.

# An Automated Approach to Counting Coughs

Julie Amendola, Octav Chipara PhD, Alberto Segre PhD, Doug Hornick MD, Alejandro Comellas MD, Philip Polgreen MD

#### Background

Coughing is a prominent feature of Cystic Fibrosis (CF) and increased levels of coughing often signal exacerbations of the disease. CF exacerbations can increase the progression of the disease and decrease quality of life. Current treatment guidelines recommend treating patients with antibiotics and hospitalization is often required. During the clinical course of exacerbations, clinical improvement is often difficult to track. Thus, there is a need for novel approaches to monitor clinical improvement. The overarching goal of this study is to explore cough frequency as a marker of clinical improvement in CF patients. To measure cough frequency, our research team is creating a cough-counting algorithm based on a large sample of coughing sound files collected in a variety of settings.

#### **Specific Aims**

- 1. Collect an assortment of cough recordings in a variety of settings.
- 2. Use the cough recordings to build a classifier to count coughs and determine coughing frequency.
- **3.** Determine if the average number coughs per hour during hospitalizations for patients admitted with CF exacerbations decreases during the hospital stay.

Hypothesis: Our hypothesis was that the average number of coughs per hour will decrease from the first day of data collection to the last day of data collection for patients admitted with a CF exacerbation.

#### Method

Stage 1: Outpatient Pulmonary Clinic. Patients receiving pulmonary function tests were recruited and consented. Cough sounds were recorded during pulmonary function tests using a custom recording application. The collected cough sounds were annotated using our custom annotation software.

Stage 2: QuickCare Clinic. After receiving a non-human-subjects determination, microphones and recording devices were placed in waiting rooms of four UI QuickCare clinics in Iowa City, Coralville and North Liberty. The microphones recorded all sounds from 8am to 5pm in the sitting areas of the waiting rooms. A portion of the data collected was annotated using the custom annotation software.

Stage 3: Inpatient Pulmonary Unit. Patients who were admitted for cystic fibrosis, COPD, or pneumonia were recruited to participate for the course of their hospital stay. After obtaining consent from patients, a microphone and recording device were placed in their room and recorded sound for 24 hours per day. Sound data were collected until the patient was discharged. In addition, each day the patients were asked to self-report how they were feeling overall and the severity of their cough on a scale from 1 to 10, and if their coughs were productive.

#### Results

We collected data on 500 patients in stage 1, for 40 total days in stage 2, and for 15 patients in stage 3. Based on the data collected in Stage 1 of our project, we built a Random Forest Classifier to classify whether 400 ms segments of audio included a cough or not. We trained the classifier on 80% of the data and we report the results on the testing set that includes the remaining 20% of the data. The area under the ROC curve was 0.958 with a precision of .80 and a sensitivity of 0.72. The vast majority of false positives and false negatives were due to problems associated with annotations (e.g., post-cough periods associated with coughs).

#### Conclusion

The cough counting algorithm that we have developed is promising. By correcting our annotation approaches we expect to be able to improve our results considerably. An accurate cough counting tool will help monitor the clinical progress of not only patients with CF, but also a large number of other clinical diseases presenting with coughs.

#### High- and Total- Spinal Anesthesia: A Systematic Review

#### Erik Anderson MA, Michael Heffernan, Christopher Childs, Unyime Ituk MD, Cynthia Wong MD

#### Introduction:

High- or Total Spinal Anesthesia is a rare yet serious complication of spinal or epidural anesthesia. Currently there is only a reported incidence rate of 1:4,336 during neuraxial procedures for the obstetric population, but there is little to no data for the general population.<sup>1</sup> Most of current information is reported through case reports and case series, but this does not describe populations or conditions that may make a patient more susceptible to total spinal anesthesia. The use of neuraxial blocks such as epidural and spinal anesthesia are some of the most commonly used forms of anesthesia. In the United States, nearly 66% of mothers will use some form of neuraxial anesthesia for pain relief during childbirth.<sup>2</sup> Neuraxial anesthesia is used in multiple other procedures such as gastrointestinal, gynecological, orthopedic, thoracic, urological, or vascular surgery.<sup>3</sup> There are multiple techniques that are under the scope of neuraxial anesthesia such as spinal anesthesia, epidural anesthesia, combined spinalepidural, and caudal anesthesia.

There are multiple potential complications that could arise from neuraxial anesthesia including, but not limited to, systemic toxicity, hypotension, inadequate block, or respiratory depression.<sup>4</sup> A serious complication of spinal or epidural anesthesia is total- or high spinal anesthesia. Total- or high spinal anesthesia can be caused by excessive doses of an anesthetic agent, incorrect placement of the epidural catheter, failure by the clinician to decrease the dosage, and anesthetic for at-risk patients such as elderly, pregnant, obese, or short stature patients.<sup>4</sup> During an episode of high-spinal anesthesia, there is paralysis of cervical nerves, C3-C5, while during a totalanesthesia episode, the block goes high enough to affect the cranial nerves in the brainstem.<sup>4</sup> Consequences of the paralysis of these structures leads to unconsciousness, apnea, hypotension, as well as anterior spinal artery syndrome.<sup>4</sup> There is currently no cure or reversal for this complication, therefore, physicians must manage the symptoms until the anesthetic is metabolized. This is generally done through mechanical ventilation to maintain an airway, as well as provide cardiovascular support and pharmacological therapies that can be used to treat hypotension and bradycardia.4

#### **Methods:**

This study was conducted following the PRISMA guidelines. To conduct the initial search, we closely worked with the librarian to harvest MeSH terms who then formed the search strategies for PubMed, EMBASE, CINHAL, Web of Science, and Cochrane. Additionally, searches were completed in Google Scholar by searching "High Spinal Anesthesia" and "Total Spinal Anesthesia". We manually searched for all of the Report on Confidential Enquiries from Maternal Deaths from 1970 to 2017 as well as manually searched "Anesthesia Closed Claims" in PubMed. From these searches, we acquired 4,721 sources which were then imported into EndNote. We used the PRISMA Flow Diagram to guide our screening process which is found on their website. Of the 4,721 articles found, a total of 91 articles were considered eligible for the study. Each article was then read and the following data was recorded: the patient's age, sex, Gravida and Parity (if applicable), height, weight, BMI, primary procedure, type of neuraxial anesthesia, level at which the neuraxial anesthesia was given, medications used, dosage of medication, first symptom presented, other symptoms seen, if the patient lost consciousness, intervention, time until resolution, clinical scenario, complications, and previous medical conditions. Some of the sources that were found were retrospective studies which gave us the incidence rate of high- or total- spinal anesthesia from their perspective studies.

#### **Results:**

From our data, there were a total of 125 cases from 90 authors and 30 different incidence rates presented in retrospective from 17 authors. Of the eligible cases, the average age was 34 years old, composed of 80% women. 58 of the cases occurred during labor, 15 during caesarian sections, 4 during gynecological procedures, 5 during anesthesia procedures, 9 during general surgeries, 10 during orthopedic surgeries, 4 during urological surgeries, 6 during vascular surgeries, and one during a plastic surgery, cardiovascular surgery and gastrointestinal procedure. Additionally, high or total spinal anesthesia occurred, 54 times with epidural anesthesia, 24 times with spinal anesthesia, 20 times with combined spinal epidural anesthesia, 2 times with a double catheter epidural and 3 times with caudal anesthesia.

#### **Conclusion:**

From these results we hope to help educate physicians about the risks of this rare complication. We would also This study has the potential to give future health care professionals the tools to better assess a patient's risk for total- or high-spinal anesthesia and develop best practices to mitigate this risk and management of patients when this adverse event occurs.

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**Project title:** The Effect of Individualized Positive End-Expiratory Pressure Compared to Low Positive End-Expiratory Pressure on Tissue Oxygenation During One Lung Ventilation in Obese Patients undergoing Thoracic Surgery

Student: Nolan Asprey, B.A. Mentor: Dionne Peacher, M.D. Co-mentors: Kenichi Ueda, M.D., Ph.D., David Kaczka, M.D., Ph.D.

**Background:** One lung ventilation (OLV) is a common technique used during thoracic surgery to facilitate surgical exposure. Although most patients can tolerate OLV, certain patient characteristics, such as obesity, increase the risk for developing hypoxemia which has a multitude of negative effects on end organ function.

Lung recruitment followed by low positive end-expiratory pressure (PEEP, 5-8 cmH<sub>2</sub>O) during OLV is shown to be effective to reduce atelectasis (closure of lung airspaces) on the non-operative lung. Alternatively, other studies have suggested that titrated PEEP may increase arterial oxygenation and decrease hypoxemia more effectively than low PEEP. Applying higher (titrated or individualized) PEEP could negatively impact cardiac output and thereby organ and tissue oxygenation. In obese patients, much higher PEEP could be necessary to achieve individualized PEEP level which may significantly reduce cardiac output.

**Purpose**: Our study investigated the effect of individualized PEEP on tissue oxygenation (using near-infrared spectroscopy cerebral oximetry) compared to low PEEP, in obese patients, during OLV. The primary outcome was cerebral O<sub>2</sub> saturation. Secondary outcomes were mean arterial pressure and total phenylephrine dose.

**Methods**: In this single-center, prospective cross-over trial, adult patients with body mass index (BMI)  $\geq$  30 kg/m<sup>2</sup> undergoing open or thoracoscopic pulmonary lobectomy were studied. Intraoperatively, after initiation of OLV (with tidal volume 5 ml/kg ideal body weight) and surgical incision, a lung recruitment maneuver (positive pressure breath held at 35 cmH<sub>2</sub>O for 15 seconds) and a decremental PEEP titration (from PEEP 19 to 5 cmH<sub>2</sub>O, in decrements of 2 cmH<sub>2</sub>O every 30 seconds) were performed to determine individualized PEEP. Individualized PEEP was defined as the PEEP which corresponded to peak dynamic lung compliance. Following this titration, the patient was placed on low PEEP or individualized PEEP for a period of 20 minutes. After the first 20-minute period, a recruitment maneuver was repeated and OLV resumed with the alternate PEEP (low or individualized) level. The primary outcome was near-infrared spectroscopy cerebral oximetry (ForeSight®, Branford, Connecticut) at the end of each experimental period. Secondary outcomes were mean arterial pressure and total phenylephrine dose at the end of each experimental period. Descriptive statistics were performed for age, BMI, individualized PEEP. Paired t-test was performed for cerebral O<sub>2</sub> saturation, mean arterial pressure, peak airway pressure, mean airway pressure, and total phenylephrine dose during one-lung ventilation with low PEEP vs individualized PEEP.

**Results:** Eight patients underwent the study protocol (7 female, 1 male). Six patients underwent thoracoscopic surgery, and two patients underwent thoracotomy. Mean age was  $56.1 \pm 11.3$  years (mean  $\pm$  SD). Mean BMI was  $40.2 \pm 5.4$  kg/m<sup>2</sup>. The mean individualized PEEP in the group was  $12.3 \pm 4.3$  cmH<sub>2</sub>O. Median PEEP was 11 cmH<sub>2</sub>O. There was no significant difference in cerebral O<sub>2</sub> saturation between low PEEP and individualized PEEP (p= 0.33), mean arterial pressure (p=0.49), SpO<sub>2</sub> (p=0.86), peak airway pressure (p=0.13), or total phenylephrine dose (p= 0.95). Mean airway pressure was higher during ventilation with individualized PEEP (mean difference =  $5.5 \pm 3.2$  cmH2O, p = 0.002, 95% Cl 2.9 to 8.1).

**Conclusions:** In this preliminary interim analysis, there was no significant difference in the primary outcome of cerebral O<sub>2</sub> saturation between ventilation with low PEEP compared with individualized PEEP. In this patient population, individualized PEEP was consistently higher than low PEEP of 5 cmH<sub>2</sub>O. There was also no difference in secondary outcomes (mean arterial pressure and total phenylephrine dose). Peak airway pressures were similar, while mean airway pressure was higher during individualized PEEP. These preliminary results suggest that utilizing individualized PEEP during one-lung ventilation during thoracic surgery in obese patients does not have an adverse effect on brain tissue perfusion, arterial blood pressure, or vasopressor use.

# Evaluating the need for routine screening of carcinoid heart disease

**Student:** Olivia Atari, M1 **Mentor:** Dr. Mohammad Bashir, MD

**Background:** Carcinoid heart disease is defined as heart complications, specifically valvular destruction, resulting from carcinoid syndrome. Carcinoid syndrome is the result of neuroendocrine tumors that metastasize to the liver and release vasoactive substances into systemic circulation. Although it is clear that carcinoid syndrome often leads to heart disease, there is no consensus on screening guidelines.

**Purpose:** Patients with malignant carcinoid tumors (carcinoid syndrome) are not receiving adequate cardiac evaluation and are vulnerable to have undiagnosed carcinoid heart disease. Additionally, patients with carcinoid syndrome should receive routine screening for carcinoid heart disease. This study aimed to determine what percentage of patients are receiving cardiac workup, if this is adequate, and if there is indeed a need for routine screening guidelines.

**Methods:** The study involved a retrospective collection of data by chart review of a group of University of Hospital and Clinics patients who received non-cardiac surgery for carcinoid syndrome. A database of patients, who were treated by UIHC surgeons Dr. Odo and Dr. Howe, were reviewed by accessing their electronic medical records via EPIC. We reviewed, among others, the following variables: liver metastasis, serotonin levels, symptoms of heart disease (edema, ascites, shortness of breath, and chest pain), as well as if the patient had an abnormal echocardiogram. Using these variables, we evaluated if they met recommended criteria for echocardiogram screening, if they were screened, and if they were referred to cardiology and/or cardiothoracic surgery.

**Results:** Of the 365 patients that were reviewed 231 patients (63.3%) had liver metastasis. 14 patients with liver mets had a prior echo, 32 of the 231 (13.9%) had an echo after presenting with their tumor, and only 12 of the 231 (5.2%) had a follow up echo. 144 of the 365 patients reviewed (39.5%) had serotonin levels greater than three times the normal value. Two of these 144 had an echo prior to presentation, and only 20 of the 144 patients (13.9%) had an echo after presentation. 31 of 365 had edema, 10 of 365 had chest pain, 18 of 365 had shortness of breath, and 44 of 365 had ascites. 42 patients of the 365 had an abnormal echo result. 10 of the 42 patients (23.8%) with their initial echo abnormal, and 3 patients without initial echo results had a follow up echo. Of these 13 patients that had a follow up echo, 9 were abnormal (69.2%). 15 of the 42 patients had one or more symptoms (35.7%). 4 of the 9 patients had one or more symptoms (44.4%). 18 of the 42 (42.9%) and 6 of the 9 (66.7%) patients had serotonin levels at least three times greater than normal. 6 of the 42 (14.3%) were referred to cardiology, 4 of the 42 (9.5%) were referred to cardiothoracic surgery. 3 of the 9 patients with an abnormal follow up echo were referred to cardiology and 3 of the 9 were referred to cardiothoracic surgery (33.3%). 6 patients 12 of the 365 patients were referred to cardiology (50%), 4 of these 12 and an additional patient were referred to cardiothoracic surgery. Ultimately only 4 patients received surgical treatment and 8 patients received medical treatment for the carcinoid heart disease.

**Future plans:** The remainder of the patients from the database will need to be reviewed to add sufficient power to our study. After the data analysis is complete we will be able to determine if these values are significant, providing evidence towards the need for guidelines for routine echocardiogram screening in patients that meet these criteria. Failures at points of screening and referrals in patients that met the cardiac workup and care is inadequate and would lend support to the idea that a protocol is needed. Guidelines for screening could raise awareness and educate both patients and physicians, and potentially reduce the morbidity and mortality of patients with carcinoid syndrome.

#### Accuracy of Vaginal pH Testing Before and After Addition of Sterile Saline

Sarah Bakir, M2 Abbey Hardy-Fairbanks, MD; Colleen Stockdale, MD, MS Department of Obstetrics and Gynecology

#### **Background and Introduction**

Complaints of vaginal discharge are a common, nonspecific symptom that may suggest gynecologic infection or alteration in vaginal flora. Laboratory findings are used in the diagnosis of vaginitis, as clinical signs may not always be present or specific. Vaginal pH evaluation is a widely used point of care test that aids in the diagnosis for multiple specific conditions such as bacterial vaginosis, vaginitis, or atrophy. Because vaginal pH may indicate etiology of abnormal vaginal discharge, a timely, effective and accurate assessment is necessary. At the University of Iowa Hospitals and Clinics, typical practice includes obtaining a sample of vaginal fluid with a cotton-tip applicator and immediately placing the cotton tip within a vial of saline as preparation for a vaginal wet mount. This sample is then taken to a laboratory room and immediately the pH is tested with pH paper and a wet mount done if indicated. Since vaginal secretions are mixed with saline, there is concern that this artificially alters the pH, therefore affecting subsequent diagnoses. The recommended testing for vaginal pH is application of the pH test paper to fluid (discharge) at the posterior lateral vaginal wall. Immediate testing, without the application of saline, is considered the gold standard. This is problematic given that pH paper must be kept dry, out of light and maintained in accordance with point of care testing regulations.

#### Aims

Study aims to assess the accuracy of pH measurements after the application of sterile saline to the vaginal discharge sample as compared the gold standard of immediate testing of vaginal pH.

#### Hypothesis

Vaginal pH measurements between the two tests will be not be significantly dissimilar and thus the practice of application of saline as is practice at UIHC can continue.

#### Methods

Women between the ages of 18-80 years old who receive care at the UIHC Women's Health Clinic and have a planned speculum exam as part of their care were eligible to participate. Women seen at UIHC Women's Health Center for any complaint were approached between July and August 2018. All study activities began after approval via the University of Iowa IRB. After review and signed consent, the subject underwent routine health care examination. During the speculum examination two cotton-tip applicators were simultaneously used to collect vaginal discharge. One cotton-tip applicator was placed in a tube containing a standardized amount (5 drops) of 0.9% sterile saline. The other sample of discharge was applied immediately to pH paper. Following completion of the physical examination, the researcher took the second sample to a laboratory in the clinic and the pH of the cotton-tip applicator with vaginal discharge was tested. Both samples were immediately discarded. The subject's medical record was also used to abstract data, including age, menopausal status, use of vaginal or supplemental hormone therapy, vaginal medication use, recent antibiotic use, vaginal discharge complaints, and recent STI diagnosis/treatment. Data was compiled and stored in REDCap, a secure web-based database. Wilcoxon signed-rank test used for comparison of the two tests with p <0.05 considered significant.

#### Results

28 women consented to participate and completed collection of vaginal discharge. Age of participants ranged from 20 to 67 and average was 37.0 (±13.5). 17.9% (5 subjects) were post-menopausal and 3 of these were on hormone replacement treatment. 2 subjects (11.8%) were pregnant at the time of participation. 14 (50.0%) used physician prescribed or placed contraception with the most common being the hormonal intrauterine device, 42.9% (6 subjects). Average pH of vaginal discharge when immediately tested was 4.64 (±0.38) and 5.089 (±0.45) after application of saline. The average difference between samples was 0.45 (±0.28). In only 11% of samples was the pH result the same. Wilcoxon signed-rank test comparing the two methods of pH measurement showed them to be significantly different, p<0.0001. This showed that in 22 samples out of 28, 79% (95% CI: 63%, 94%) of the time the addition of saline resulted in a pH of 0.5 higher than the gold standard of pH testing in the room. In 2 of the samples, the saline-first test resulted in a pH of 1.0 higher.

#### **Discussion and Conclusions**

This study demonstrates that there is a significant difference in the results of pH testing when done immediately after collection and following submersion in saline. The majority of samples differed by a pH of 0.5. Further work is planned to analyze the results by multiple simulations of similar distributions to determine if rather than changing clinical practice in our clinic, the result of a saline-submerged sample can be converted by subtracting 0.5 from the result, given the high proportion with a difference of 0.5+ pH. With only 28 samples, it is possible this proportion could be lower, with 95% lower limit of 63%. More samples will have to be tested to obtain a better estimate of the proportion of saline test samples that result in a higher pH value than the in-room test samples.

# Influence of activity-induced fatigue on perceived levels of fatigue and pain, and blood lactate levels in healthy controls and chronic pain individuals

Kayla Bartos, BS; Dana Dailey, PT, PhD; Laura Frey Law MPT, MS, PhD; Dan Wang, MS; Carol Vance, PT, PhD; Kathleen Sluka, PT, PhD, FAPTA

**BACKGROUND:** Fatigue has rarely been a primary focus in clinical trials in individuals with FM and chronic pain, despite its particular role in FM individuals as a significant contributor to disease impact and dysfunction. Few validated fatigue assessments or biomarkers are characterized for use in clinical trials. Activity-induced fatigue is a significant problem that impacts function and participation in daily activities. Currently, use of standard questionnaire assessments are used to characterize the multidimensional nature of fatigue. However, the degree to which activity enhances fatigue, locally and systemically, is unknown. We suggest that physical fatigue, induced by activity, is unique and may have different underlying mechanisms. One proposed mechanism associated with activity-induced fatigue is increased circulating lactate, as lactate is released by exercising muscle. The development and validation of a lower extremity test of activity-evoked fatigue, and the role of lactate in this response, will guide future research with FM individuals, but possibly with other individuals reporting chronic pain.

#### **AIMS/HYPOTHESIS:**

Aim 1: To develop an optimal fatigue task for the lower extremities in people with fibromyalgia and chronic lower back pain and compare to healthy controls.

Aim 2: To determine the extent of fatigue across multiple dimensions before and after the lower extremity fatigue tasks in individuals with fibromyalgia, low back pain and healthy controls. We hypothesize that there will be an increase in the level of perceived fatigue and pain in people with fibromyalgia and chronic low back pain compared to the healthy controls.

Aim 3: To measure the levels of lactate systemically before and after lower extremity fatigue tasks, and to determine its relationship to fatigue. We hypothesize the levels of lactate will be increased in individuals with higher reports of fatigue compared to those with lower ratings or the healthy controls.

**METHODS:** Our goal was to assess 10 individuals each with fibromyalgia, chronic low back pain and healthy controls. Each subject was scheduled to participate in two visits, where they completed surveys using REDCap. These surveys assessed pain, fatigue, pain psychological factors, quality of life and demographics. The order of fatigue tests was assigned randomly and balanced between cohorts with 10-14 days in between for recovery. Overall activity-evoked pain, dyspnea, and fatigue intensity measurements were assessed using a 10-point number rating scale (NRS) before, during and after fatigue tests. Physical and cognitive fatigue, as well as localized fatigue and pain in the upper extremities, lower extremities, and back or neck were assessed before and after tests. Blood lactate was measured using a blood lactate meter before and after each fatigue task. The first fatigue task used a modified Astrand-Rhyming cycle ergometer test. This is a single-stage 6-minute test for that has been used to estimate VO2 max. Participants were instructed to pedal on a stationary cycle at a rate of 45 rpms at a resistance of 8 Nm for the first minute, and 60-65 rpms for the last five minutes. The second fatigue task was a modified 3-minute YMCA Step Test. This is a single-stage 3-minute test, also used for VO2 max estimations, that we modified to last 6 minutes. Each participant was instructed to step up and down from a 5.25-inch step at a rate of 24 steps/min for the first minute, and change to a step height of 8 inches for the last 5 minutes.

**RESULTS:** Initially we developed and refined the protocol for each test prior to data collection. We collected 11 healthy controls and 2 individuals with low back pain. Healthy controls had no pain before the bike or step test, while the low back pain subjects had an average pain of 3.5. After the test there were no changes in pain scores for the healthy controls, but a decrease in pain scores for the back pain subjects (average 2). Fatigue scores before the bike and step tests were 0-0.4 for the healthy controls, and increased to 0.9 for the bike test, and to 1.7 for the step test. For the back pain subjects, there was no change in fatigue scores after the bike test (0.5/1 before and after) and a small increase in fatigue for the step test (from 1/10 to 2/10). Lactate levels increased in healthy controls immediately after and 8 minutes after completion for both the bike and the step test. There were no increases in lactate for back pain subjects with the bike test, but increased lactate in 1 out of 2 subjects for the step test.

**SUMMARY:** In summary, both the bike test and the step test were well tolerated by all subjects, but the step test showed a greater increase in fatigue for both populations. Both the step test and the bike test induced increases in lactate that were not attenuated in the back pain group. Future studies involving both fatigue tests will increase the number of back pain subjects and determine if there are changes in pain and fatigue for those with fibromyalgia.

#### Cartilage Degeneration is Associated with Increased Joint Contact Stress in Patients with Hip Dysplasia

Nicholas I. Bartschat<sup>1</sup>, Holly D. Thomas-Aitken<sup>1</sup>, John C. Clohisy<sup>2</sup>, Michael C. Willey<sup>1</sup>, Jessica E. Goetz<sup>1</sup>, Robert W.

Westermann<sup>1</sup> <sup>1</sup>University of Iowa, Iowa City, IA <sup>2</sup>Washington University in St. Louis, St. Louis, MO nicholas-bartschat@uiowa.edu

**Disclosures:** N.I. Bartschat: None. H.D. Thomas-Aitken: None. J.C. Clohisy: Zimmer Biomet. M.C. Willey: None. J.E. Goetz: None. R.W. Westermann: Smith and Nephew Education.

**Introduction:** Hip dysplasia is a complex deformity of the acetabulum and/or the proximal femur that causes a pathologic mechanical environment in the hip joint. This altered mechanical state often results in hip pain and joint degeneration at a young age.<sup>1</sup> The accelerated joint degeneration and osteoarthritis development in this patient population is frequently associated with elevated cartilage contact stresses, which can be accurately predicted with computational modeling techniques.<sup>2</sup> However, the exact relationship between joint contact stresses in the dysplastic hip and locations of acetabular cartilage degeneration has yet to be investigated. The purpose of this study was to determine the association between joint contact stresses and areas of significant cartilage damage in patients with dysplasia using computational modeling and intraarticular findings.

**Methods:** Under IRB approval, patient-specific hip models were generated from pre-operative CT scans using a validated methodology<sup>2</sup>. Each patient model was aligned to the coordinate system defined by Bergmann, et al.<sup>3</sup> and loaded with a dysplastic gait cycle.<sup>4</sup> The forces applied to each model were scaled based on the patient's body mass. Discrete element analysis (DEA) was used to compute contact stresses during 13 static time-points of stance phase of gait. Contact stresses above a damage threshold  $P_d \ge 2$  MPa (as was previously determined for patients with hip dysplasia<sup>1</sup>) were considered deleterious, and the deleterious contact stresses at each of the 13 time-points were summed over the time spent in each static phase to obtain the cumulative contact stress-time over-exposure<sup>1</sup> during a gait cycle. The peak cumulative contact stress-time over-exposure<sup>1</sup> during a gait cycle. The peak cumulative contact stress-time over-exposure anterior central, anterior peripheral, superolateral central, superolateral peripheral, posterior central, and posterior peripheral.

At the time of surgery, a single hip surgeon (JCC) arthroscopically evaluated the extent of acetabular cartilage damage in each of the six regions for each patient using the chondromalacia grading scale of Beck, et al.<sup>5</sup> Zonal chondromalacia grades were then compared with the peak cumulative contact stress-time over-exposures for each acetabular region. Two-sided Wilcoxon rank sum tests with Holm-Bonferroni corrections for multiple comparisons were performed to compare differences between contact stress among the different acetabular regions and significance was set to p<0.05.

**Results:** The average peak cumulative contact stress-time over-exposure in the anterior peripheral and superolateral peripheral regions were  $4.5\pm2.0$  MPa-s and  $4.9\pm1.6$  MPa-s, respectively, significantly (p<0.001) higher than that in the anterior central, superolateral central, posterior central, and posterior peripheral regions ( $0.7\pm0.9$  MPa-s,  $1.4\pm1.1$  MPa-s,  $0.1\pm0.2$  MPa-s, and  $0.5\pm0.8$  MPa-s, respectively). The average chondromalacia grade in the anterior peripheral region was  $2.3\pm1.3$ , which was significantly (p<0.001) higher that in the anterior central region ( $1.0\pm0.0$ ). The average chondromalacia grade in the superolateral peripheral region was  $3.1\pm1.0$ , which was significantly (p<0.001) higher that in the anterior central, superolateral central, posterior central, and posterior peripheral regions ( $1.0\pm0.0$ ). The average chondromalacia grade in the superolateral peripheral region was  $3.1\pm1.0$ , which was significantly (p<0.001) higher that in the anterior central, superolateral central, posterior central, and posterior peripheral regions ( $1.0\pm0.0$ ,  $1.1\pm0.4$ ,  $1.1\pm0.4$ , and  $1.4\pm0.8$ , respectively). Additionally, damage to the acetabular cartilage began when average peak contact stress-time over-exposures were within the range of 2-4 MPa-s.

**Discussion:** There appears to be a positive association between exposure to deleterious contact stresses and extent of cartilage damage. Both the average peak cumulative contact stress-time over-exposure and the average chondromalacia grade were highest in the superolateral peripheral and anterior peripheral regions, which confirms previous findings that articular cartilage damage is most common in these acetabular regions<sup>6</sup> and validates the use of DEA-computed contact stress information for identifying regions of tissue damage in dysplasia. These results illustrate the benefit of offloading certain regions of the hip seeing excess contact via corrective surgery to mitigate further cartilage damage to preserve the native hip.

**Significance:** High levels of deleterious contact stresses computed using DEA are associated with increased articular cartilage damage in dysplastic hips, indicating that corrective surgery should aim to maximally decrease these contact stresses to prevent further joint degeneration.

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# Anterior versus posterior total hip arthroplasty: A comparison of outcomes at an academic institution.

Bertsch ML, Clark CR, Otero JE

# BACKGROUND:

In the last 20 years, the anterior approach for total hip arthroplasty (THA) has become increasingly popular among arthroplasty surgeons and patients. This is due in part to belief that this approach allows for faster recovery, shorter hospital stays, and improved hip stability when compared to the posterior approach, yet these potential benefits continue to be debated. In this study, our goal is to compare short term perioperative complications and readmission rates between anterior and posterior THA performed by experienced arthroplasty surgeons at a single academic institution.

# **METHODS:**

Patients who underwent THA between 2016 and 2017 by experienced arthroplasty surgeons were identified in our hospital database. Patient demographics and comorbidities were compared in the 2 cohorts (anterior approach versus posterior approach), and subsequent univariate and multivariate analyses were used to determine risk factors for complications and readmission in the 30-day postoperative period.

# **RESULTS:**

We identified 316 eligible THA patients; 170 underwent anterior approach, and 145 underwent posterior approach. Patients who had posterior approach had higher BMI (30.8 vs. 27.8) and shorter operative times (95.7 vs. 124.9 minutes) (P <.001), but were not statistically different with respect to age, sex, diabetes, etc.. Univariate analysis revealed that patients with posterior approach had longer hospital length of stay (2.6 vs 1.7 days, P < .001), higher rates of wound complication (3.47% vs. 0%, P = 0.020), overall complication (12.5% vs. 2.4%, P < .001) and readmission (6.25% vs. 1.18%, P = 0.027). Multivariate regression analysis identified posterior approach (adjusted odds ratio 6.94, 95% confidence interval 2.12 - 22.71) as the only independent risk factor for 30-day complications.

# CONCLUSIONS:

In a cohort of patients who underwent THA through the anterior approach or the posterior approach at an academic institution, anterior approach was associated with favorable complication and readmission rates.

Leishmania major and Staphylococcus aureus coinfection in mice and human neutrophils

Jayden Bowen, Tiffany Borbon, Diogo Garcia-Valadares, Cory Parlet, Yani Chen, Bayan Zhanbolat, and Mary Wilson

**Introduction:** Cutaneous leishmaniasis (CL) is a vector-borne neglected tropical disease resulting in persistent and often disfiguring skin lesions. *Leishmania major* is an obligate intracellular protozoan and an important cause of CL in the Eastern hemisphere. Recent work has suggested that microbial communities present at the site of *Leishmania* infection play a role in shaping the subsequent immune response. *Staphylococcus aureus* is a bacterium often cultured from CL lesions and a member of the human microbiome that asymptomatically colonizes human skin and nasal cavities. Furthermore, *S. aureus* is among the microbes in the gut of the insect vector for CL due to *L. major* and could be co-inoculated with the parasite into host skin.

**Purpose:** We hypothesized that the presence of *S. aureus* at the site of inoculation with *L. major* influences pathogenesis and modifies the host response to *L. major* infection.

**Methods:** *S. aureus* was co-introduced at the time of *L. major* infection intradermally in the skin of C57Bl/6 mice. The pathologic immune response was quantified by measurement of the resulting lesions. *S. aureus* burdens were measured by *in vivo* imaging of luciferase activity. *S. aureus* expressing GFP and *L. major* expressing mCherry were inoculated intradermally. One day later, the skin was disrupted and then analyzed by flow cytometry. Human neutrophils were isolated from whole blood using dextran sedimentation and FicoII density gradient centrifugation. The neutrophils were then cultured for 60 minutes with GFP+ *S. aureus* and mCherry+ *L. major*, then treated for 30 minutes with gentamycin to remove extracellular bacteria before pathogen uptake was quantified by flow cytometry.

**Results**: We observed that the presence of *S. aureus* at the time of infection exacerbated the pathologic immune response compared to either pathogen alone. Utilizing *in vivo* imaging, we found that *S. aureus* burdens were increased during the first three days of coinfection compared to *S. aureus* alone. Flow cytometry of mice coinfected for 24h revealed a population of myeloid cells containing both *S. aureus* and *L. major*, of which 90% or more were neutrophils. To investigate relevance to human infection, we coinfected primary human neutrophils. Coinfection increased uptake of both *S. aureus* and *L. major* compared to single infection with either pathogen, and a subset of infected neutrophils (~5%) contained both pathogens.

**Conclusions:** These data suggest that *S. aureus-L. major* coinfection promotes *in vivo* replication of *S. aureus* in mice, and that pathogen uptake by neutrophils is increased during coinfection both *in vivo* in mice, and *in vitro* in human neutrophils. These data lead us to hypothesize that neutrophils containing both *S. aureus* and *L. major* play a role in exacerbating the early stages of coinfection.

# FORECASTING AUTISM GENE DISCOVERY WITH MACHINE LEARNING AND HETEROGENEOUS BIOLOGICAL DATA

L Brueggeman<sup>1</sup>, T Koomar<sup>1</sup>, J Michaelson<sup>1</sup>,<sup>2</sup>

<sup>1</sup> Interdisciplinary Genetics Program, University of Iowa

<sup>2</sup> Department of Psychiatry, University of Iowa

Genes have been one of the most effective windows into the biology of autism, and it has been estimated that perhaps a thousand or more genes may confer risk. However, only 75 genes are currently viewed as having robust enough evidence to be considered true "autism genes". While massive genetic studies are underway to produce data to implicate additional genes, alternative approaches have aimed to predict autism risk genes using other forms of genomescale data, such as gene expression and network interactions. Here we present forecASD, which is a machine learning approach that integrates spatiotemporal gene expression, heterogeneous network data, and previous gene-level predictors of autism association to yield a single score that represents each gene's likelihood of being involved in the etiology of autism. We demonstrate that forecASD has substantially increased performance compared to previous gene-level predictors of autism association, including genetic-based measures such as TADA. On an independent test set, consisting of newly-released data from the SPARK, we show that forecASD best predicts which genes will have an excess of LGD mutations. Furthermore, we define a set of functional pathways that are currently underrepresented in the autism literature.

#### Recovery from cesarean delivery at UIHC: a comparison to Enhanced Recovery Protocols

Student: Grace Chabal Mentor: Dr. Noelle Bowdler, MD Collaborators: Dr. Donna Santillan, PhD

**Introduction:** Enhanced Recovery After Surgery programs (ERAS) have been used by some specialties for years, and are now becoming popular for gynecologic and obstetrics surgeries. ERAS programs consist of evidence-based interventions during a patient's hospital stay that are intended to promote early return to activities such as eating, ambulation, and voiding and to manage pain. These programs reduce the risk of complications post-operatively and shorten a patient's hospital stay. The University of Iowa Hospitals and Clinics (UIHC) is developing an ERAS protocol for cesarean deliveries. Our goal was to determine how current practices and outcomes for cesarean deliveries at UIHC compare to established ERAS programs. We also sought to identify which patients would be appropriate candidates for an ERAS protocol at UIHC.

**Methods:** We collected 115 data elements from the EPIC electronic medical records of 206 patients who had a scheduled cesarean delivery in the year 2017. Patients were excluded if they had a morbidly adherent placenta or multiple gestation, or they delivered before 35 weeks gestation. We calculated the average time to reach post-operative goals for our sample, and then grouped our sample by gestational age at delivery and indication(s) for cesarean delivery in order to make comparisons to identify which groups would be good candidates for ERAS.

**Results:** The average times to meet postoperative goals for our sample including first ambulation, urinary catheter removal, first liquid intake, and first solid intake were: 14.63 hours, 19.82 hours, 2.73 hours and 5.59 hours, respectively. Our patients were without oral liquids and solids for over 12 hours before surgery. Comparisons of women who delivered at different gestational ages showed significantly different indications for cesarean delivery, rates of intra-operative complications, blood loss, birth weights, and newborn disposition. Time to meet postoperative goals did not differ between groups except for time to ambulation, which was shorter for women who delivered at earlier gestational ages. Groups separated by indication(s) for surgery differed significantly with respect to gravidity, parity, primary cesarean, secondary cesarean, gestational age at delivery, intraoperative complications, and newborn disposition.

**Discussion:** The time for UIHC patients to meet post-operative goals is longer than stated in established ERAS protocols. Preoperatively, patients were without oral liquids and solids for longer than recommended by ERAS programs. Some practices at UIHC already resembled aspects of ERAS, such as active warming during surgery and neuraxial morphine for post-operative analgesia. Many of the differences between groups by gestational age and indication(s) for surgery were expected. However, there were more intraoperative complications, in particular postpartum hemorrhages, in deliveries at earlier gestational ages. This might be explained by the differences in indications for delivery at various gestational ages; women with placenta previas were delivered at 36 weeks gestation whereas repeat cesarean sections were scheduled at 39 weeks gestation.

**Conclusions:** We hypothesize that the times to meet postoperative goals after cesarean section could be shortened by implementing an ERAS program at UIHC. Based on our comparisons between groups by gestational age and indication(s) for delivery, any patient who meets our inclusion criteria could benefit from ERAS interventions. However, expectations for the neonates delivered at 35-36 weeks may differ from those at 37+ weeks. For example, a goal such as skin to skin contact with their mothers in the operating room may have less success as there is a greater likelihood that these infants would require care in the neonatal intensive care unit shortly after birth.

#### The Genetics of Melanoma in a Veteran Population

Kevin Cheung, M2 Mentor: Jennifer Powers, MD

#### Introduction:

Melanoma is the fifth most common cause of cancer in the United States, and in 2013, it resulted in over 9000 deaths. Moreover, military personnel have disproportionately greater risk of developing melanoma. A case-control study in 1984 showed that a significantly greater percentage of melanoma patients were stationed in the tropics during World War II compared to age-matched control subjects without exposure to equatorial sunlight (34% compared to 6%). Military personnel are exposed to varying environmental factors, and as a result, underlying pathogenic mutations and mechanisms involved in the development of melanoma is suspected to be different compared to the general population.

# **Problem Statement:**

Because military personnel face unique exposures, determining the genetic predisposition of melanoma in the military population may help inform clinical decisions to pursue gene-specific testing and treatment. We hypothesize that VA melanoma samples will demonstrate a lower prevalence of BRAF and NRAS mutations and a higher prevalence of c-KIT mutations compared to that of the general population.

#### Methods:

Tissue samples of confirmed melanoma cases in a 7-year period between January 1, 2010 to January 1, 2017 were obtained from the Iowa City VAMC and analyzed by massively parallel or next generation sequencing (NGS). Results are based on statistical analysis of gene sequencing data and clinical data collected from medical records.

#### **Results:**

Samples were collected from 185 patients admitted to the VA for treatment of melanoma. The sample population was 97% male, and 92% identified as white, non-Hispanic. The average age at melanoma diagnosis was 68. Of all patients, 97 (52%) had a positive history of previous skin cancer with 35 (19%) positive for previous melanoma. Nine patients (5%) had a positive family history of melanoma. Staging data was available for 169 patients, and of those, 116 (69%) had stage one melanoma and 8 (4%) had confirmed stage 3 or 4 melanoma. For treatment, 26 (14%) of patients received care other than or in addition to wide local excision, including radiation, immunotherapy, targeted therapy, or clinical monitoring. The samples included 15 patients who were tested for BRAF mutation with about half (7) who tested positive for the mutation, and ultimately, 5 who received BRAF-targeted therapy.

# Conclusions:

In this study, about half of patients who received BRAF testing tested positive, which resonates with the general population. However, more genetic information will be available from pending results of NGS analysis. Furthermore, only 5 individuals received BRAF-targeted therapy, and none received targeted treatment for other associated mutations. With greater understanding of the genetics of melanoma in the military population, more targeted therapies may be pursued resulting in potentially better outcomes for patients.

# Characterization of Adenovirus Mediated Gene Delivery into the Cochlea

Joseph J. Chin, Stacia L. Phillips, Lintao Gu, Linjing Xu, Marlan R. Hansen, Samuel M. Young

# Background:

Hearing loss is the most common sensory deficit. While there are multiple mechanisms behind hearing loss, many etiologies have a genetic component. In developed countries, approximately 1 in 500 newborns have hearing loss, with 80% of these prelingual cases being genetic in nature. In addition, animal work suggests that activation and inactivation of key genes can prevent certain types of environmental (acquired) cases of hearing loss such as noise induced hearing loss. Thus, gene therapy is an attractive candidate for potential therapeutics. However, there are obstacles that must be considered. The cochlea is difficult to work with from a surgical standpoint due to its small size, the surrounding bony labyrinth making direct access difficult, and the presence of the blood-cochlea barrier. In addition, gene therapy is a developing field and issues such as immune responses and efficiency of gene delivery must be considered.

# **Objective**:

Perform a pilot study to determine the feasibility and best method to administer helper dependent adenoviruses into the cochlea.

# Methods:

Helper dependent adenoviruses containing a cytomegalovirus (CMV) promoter, the mclover 3 fluorescent protein, and a nuclear localization tag were generated. Mice were anesthetized and the cochlea and posterior semicircular canal were exposed via post-auricular incision. The posterior semicircular canal was perforated and followed by injection of helper dependent adenoviruses via the round window membrane. Mice were then sacrificed 3 and 7 days following injection. Cochlea were extracted, fixed, and stained with antibodies to determine where the virus localized via confocal microscopy.

# **Results**:

Administration of helper dependent adenoviruses via the round window coupled with posterior semicircular canal fenestration is a feasible approach. Expression of mclover 3 was detected in the lateral wall of the cochlea and in the glia.

# Conclusion:

Helper dependent adenoviruses are a feasible vector for gene therapy. Further work will be involve optimizing the antibodies used for staining to determine the precise cell types that the adenovirus transfects, testing the long-term effects of the gene therapy, test different viral serotypes, and test different promoters.

#### The Effect of Sleep Position Preference on Periorbital Symmetry

Dabin Choi, B.S.<sup>1</sup>, Kenten D. Kingsbury, C.N.A.<sup>2</sup>, Audrey C. Ko, M.D.<sup>3</sup>, Keith D. Carter, M.D., F.A.C.S.<sup>3</sup>, and Erin M. Shriver, M.D., F.A.C.S.<sup>3</sup>

<sup>1</sup>Carver College of Medicine, University of Iowa, Iowa City, Iowa, <sup>2</sup>University of Iowa, Iowa City, Iowa <sup>3</sup>Department of Ophthalmology and Visual Sciences, University of Iowa Health Care, Iowa City, Iowa

#### **Background:**

Periorbital structures such as eyebrow and eyelid play key roles in visual function and aesthetic appearance. Sleep position preference has been shown to have a significant correlation with facial aging and symmetry in previous studies. The effect of sleep position on the eyelids and eyebrow position has not been evaluated. Knowledge of the effect of sleep position on these characteristics is crucial to understanding patients' baseline eyelid and eyebrow characteristics, surgical planning, and maximizing post-operative results.

#### Purpose of the study:

This study investigates the relationship between patients' sleep position preference and the degree of eyebrow ptosis, eyelid ptosis, and upper eyelid dermatochalasis. Our hypothesis is that patients who demonstrate a strong sleep side preference will have an ipsilateral increase in 1) upper and lower eyelid ptosis, 2) eyebrow ptosis, and 3) upper eyelid dermatochalasis. Patients who lack a strong sleep side preference will demonstrate less eyebrow and eyelid laxity and asymmetry.

#### Methods:

A prospective randomized study of consecutive patients at the University of Iowa Department of Ophthalmology and Visual Sciences was conducted in compliance with the Institutional Review Board. Eligibility criteria included the absence of any periocular-altering trauma, surgery, or disease process. Study participants were given a questionnaire to ascertain their sleep position preference. Standardized digital photographs of patients were obtained and Image J software was used to obtain positional measurements for the eyebrow and upper and lower eyelid positions. The image measurements assessed were the distance from the pupil centroid to the upper eyelid margin (MRD1; marginal reflex distance 1), the pupil centroid to the lower eyelid margin (MRD2; marginal reflex distance 2), the upper eyelid margin to the visible upper eyelid skin fold (TPS; tarsal platform show), and the pupil centroid to the superior limit of the eyebrow (BP; brow position) (Figure 1). These results were then compared to the patient reported sleep position preference to determine correlation.

#### **Results:**

A total of 84 patients who satisfied the selection criteria were evaluated, of which 32 patients preferred right side, 24 patients preferred left side, and 14 patients preferred sleeping on both sides. 14 patients who preferred supine or prone sleep position were not included in the analysis. Patients with right or left sleep side preference demonstrated significantly lower MRD1 image measurements on the side which they customarily sleep (0.34~0.39 mm; p-value<0.005). No significant differences were seen in other image measurements among patients with strong sleep side preference. Among patients who sleep on both sides, there were also no significant differences between right and left periorbital image measurements.

#### **Conclusion:**

These results suggest that patients with a predominant sleep side preference demonstrate a significant ipsilateral increase in upper eyelid ptosis. There were no differences noted in eyebrow position, amount of upper eyelid dermatochalasis, and lower eyelid position.

Jonathan W Chou, M4 PI: Gordon F Buchanan Collaborators: Alex Petrucci

### Title

Effect of dorsal raphe nucleus stimulation on post-ictal generalized EEG suppression following maximal electroshock induced seizures in mice

#### Objective

To examine the effect of dorsal raphe nucleus serotonin neuron stimulation on post-ictal generalized EEG suppression duration following maximal electroshock seizures in mice.

#### Background

Sudden unexpected death in epilepsy (SUDEP) is the most common cause of death in patients with refractory epilepsy. Although the exact etiology of SUDEP is unclear, a prolonged period of postictal generalized EEG suppression (PGES) may portend increased SUDEP risk. Abnormalities in serotonin (5-HT) signaling have been implicated in SUDEP through effects on breathing, and sleep and arousal regulation. 5-HT neurons in the dorsal raphe nucleus (DRN) are involved in sleep-wake regulation. We hypothesized that increasing 5-HT by stimulating DRN neurons before a seizure could reduce the duration of PGES.

#### Methods

Adult C57BL/6J mice were implanted with a microdialysis cannula into the DRN [AP -5.7 mm, ML 0 mm, DV: -3.12 mm, 26° angle; measurements from bregma] and EEG/EMG electrodes. Once recovered and acclimated to the recording apparatus, acidified (pH 6.8) or control (pH 7.4) artificial cerebrospinal fluid (aCSF) was perfused to the DRN for 10 min prior to acute seizure induction via maximal electroshock (MES; 10-16 mA; 0.2 s; 60 Hz; sine wave). Plethysmography, electroencephalography, and electromyography were recorded, and PGES was scored with a custom Matlab script.

#### Results

Mean PGES duration was shortened by application of acidified aCSF compared to control aCSF (21.8  $\pm$  1.5 s vs 28.9  $\pm$  1.4 s; n = 3).

#### Conclusion

Stimulation of DRN 5-HT neurons leads to decreased PGES duration following maximal electroshock in mice. Further work is required to elucidate the underlying neural pathways and critical regions involved, as well as the relationship between alterations in PGES and mortality. Ultimately, a better understanding of the underlying mechanisms may lead to interventions that reduce mortality through effects on PGES.

#### Assessing the NSQIP® Surgical Risk Calculator's Accuracy in Radical Cystectomy Outcomes

Gabriel Conley, M2 Kenneth Nepple, M.D.

#### Background

The National Surgical Quality Improvement Program (NSQIP®) Surgical Risk Calculator is a service provided by the American College of Surgeons, which was designed to enhance surgical outcomes and predict surgical complications for patients in the real-world setting. It is a prediction tool that incorporates 19 individual patient variables into each of its calculations, which guide the decision-making of physicians at nearly 700 hospitals across the United States1. While useful, it is apparent in the literature that the NSQIP® Risk Calculator's statistical and clinical potential as a prediction tool is not optimized to accurately predict outcomes for every procedure, because of the relatively few patient comorbidity/demographic criteria that it includes. These shortfalls may be intensely problematic because it's often those patient-specific factors drive treatment choice and have major effects on patient outcomes.

Cystectomy, the surgical removal of the urinary bladder to treat patients with muscle-invasive bladder cancer, is a complex procedure with a relatively high rate of suboptimal surgical outcomes (with a complication rate of approximately 64%<sub>3</sub>, which typically concern the gastrointestinal system or are infectious in nature). The combination of an unhealthy patient population and a high prevalence of complication makes the cystectomy population optimal for an evaluation of the NSQIP® Surgical Risk Calculator's accuracy. The treatment paradigm for muscle invasive bladder cancer has been primarily with cystectomy, but emerging data is suggestive of a potential role for bladder sparing with chemoradiation or chemotherapy in patients who are too high-risk for cystectomy<sub>2,3</sub> This highlights the need for a better means of predicting complication in these patients.

#### Purpose

Our project aims to evaluate the accuracy of NSQIP in predicting the surgical outcomes of an institutional cohort of cystectomy patients, and then to determine if the Risk Calculator's predictive accuracy can be improved by using variables beyond the 19 patient-specific data points that NSQIP analyzes. It is my hypothesis that the most statistically significant predictor of post-surgical outcomes in cystectomy patients is a combination of data points from NSQIP and chart-evaluated patient-specific information.

#### Method

The NSQIP® Surgical Risk Calculator currently uses 18 data points in formulating its standard surgical prediction for a given patient/procedure. After obtaining these individual data points for each patient in a 156-person cohort of cystectomy patients treated at the University of Iowa Hospitals and Clinics between 2014 - present, we conducted a NSQIP Surgical Risk calculation for each of them. We then retrospectively analyzed how these patients performed, post-operatively, and compared each of those surgical outcomes with its Surgical Risk Calculator prediction. These results were organized into tertiles of performance, and an ANOVA was performed for each adverse event (alpha =0.05). The first tertile comprises the 52 patients (one third of the cohort) with the highest risk of the event in question (serious complication, any complication, surgical site infection, readmission, and discharge to a nursing home), as calculated by NSQIP. The second tertile comprises the 52 patients with the median risk in our cohort, and the third tertile comprises numbers.

	Serious Complication	Any Complication	SSI	Readmission	Discharge to Nursing
1st Tertile	32.7 %	36.5 %	25.0 %	28.8 %	37.3 %
2nd Tertile	26.4 %	25.0 %	7.7 %	23.1 %	13.7 %
3rd Tertile	17.3 %	23.0 %	11.5 %	19.2 %	5.8 %
p-value	0.195	0.26	0.138	0.52	0.000084

#### Primary Preliminary Results, Organized Into Risk "Tertiles"

#### **Conclusion/Discussion**

As the preliminary data shows, patients in the first tertile of risk had the highest incidence of each adverse event happening, but ANOVA analysis determined that only the metric of "Discharge to a Nursing Home" achieved statistical significance. These results highlight the need to determine if other variables can be used to help assess a patient's surgical risk of complication, and our team at UIHC will perform univariate analysis to determine if we can determine what these extra criteria are, once our cohort size is large enough to generate adequate statistical power.

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# A New Rapid Visual Field Screening Test for Patients with Idiopathic Intracranial Hypertension

# David Crompton, Ramon Galindo, Dr. Michael Wall

**Introduction:** Idiopathic Intracranial Hypertension is a condition due to high pressure within the fluidfilled spaces that surround the brain. This increase in pressure can cause optic nerve edema and visual loss, which is typically monitored in patients diagnosed with the disease. The current automated perimetry methods utilized in the clinic to detect these losses aren't testing the far peripheral visual field; hence 2/3 of the visual field remains largely unexplored. Recent advances, such as the implementation of a larger stimulus size, Bayesian strategies to reduce the test time, and the recent evolution of the Open Perimetry Interface (OPI), have made testing the far peripheral field practical. Despite these advances, the complete test takes about 15 minutes per eye, and there has yet been a good screening test to detect these deficits.

**Purpose:** We have developed a method of static automated perimetry that reliably tests the complete visual field (referred to as the "threshold" test), which takes approximately 15 minutes per eye. This study aimed to compare results of the threshold test with a new "screening" test, which, using a different algorithm, only takes 4-6 minutes per eye. Our aim was to validate this test against the threshold test and determine if visual field deficits exist in the far periphery that are not detected with current methods.

**Methods:** We recruited patients from The University of Iowa's Neuro-ophthalmology clinic with a variety of optic neuropathies including idiopathic intracranial hypertension (IIH) and hemianopias; we report on those tested with IIH. Patients were required to have a visual acuity of better than 20/40 with papilledema and not have other causes for visual loss. Patients were given the threshold test, the screening test, and the standard clinical automated perimetry test in the same eye.

The number of test locations flagged at the 5% or worse level in the superior hemifield, the inferior hemifield, and the total field were counted in both the screening and the threshold tests for the 8 IIH patients. A Wilcoxon Paired Signed Rank Test was utilized to compare the groups for any statistically significant differences. A qualitative analysis was also done by determining whether there was a matching visual field defect on each of the tests. A visual field defect was defined as 3 adjacent abnormal locations at the 5% level or 2 adjacent locations with one at the 1% level in a clinically suspicious area. The percentage of missed defects (out of 16 eyes) was calculated. Visual field examinations from the threshold and screening tests were compared with the standard clinical test to detect the presence of any unnoticed deficits.

**Results:** We found the screening test missed two (out of 16) visual field defects that the threshold detected, or 12.5%. Both visual field deficits missed were mild visual loss. Two cases were observed where peripheral defects were not found with the clinical test. A Wilcoxon Paired Signed Rank Test between the screening and the threshold tests was used for the superior hemifield, inferior hemifield, and total field, and no statistically significant differences were found.

**Discussion:** We found the screening test yields similar results to the threshold test in patients with IIH while decreasing testing time by over 50% and testing of the far periphery can add clinically useful information. We plan to analyze other optic neuropathies and hemianopias to see if these findings generalize.

Title: Penalized Regression Models on the Lipid Profile of Subjects With Multiple Sclerosis

Student: Andres Dajles

Mentor: Yuan Huang, PhD

Collaborator: Ruth Grossman, PhD

**Background:** Multiple Sclerosis is an autoimmune disease that causes high levels of fatigue in patients. Under the Wahls diet, a modified paleolithic diet, patients have claimed that their levels of fatigue have been reduced. With a data set collected from nineteen subjects, we analyze the lipid profile before undergoing the diet and 12 months after. We use the difference in this lipid profile to model the change in fatigue before the diet and 12 months after.

**<u>Purpose</u>**: To infer a statistical model that predicts the variation in the change of fatigue of subjects who adhered to the Wahls diet for a year. We consider the year-change in the lipid profile of these subjects as the predictors in our model.

**Method:** Because of the high dimensionality and small sample size of the data set, we consider penalized regression models. In particular, we consider Maximum Convex Penalized models.

<u>**Results:**</u> Using Maximum Convex Penalized (MCP) regression models, we conclude that lipids <u>LysoPE</u> 22:5...<u>MH</u>...1.63" and "Unknown PC 36:4...<u>MH</u>...9.69" are statistically important in explaining the variation in the change of fatigue scores on these subjects.

<u>Conclusion:</u> From the 398 different lipids analyzed, MCP reveals that <u>LysoPE</u> 22:5...<u>MH</u>...1.63" and "Unknown PC 36:4...<u>MH</u>...9.69" are statistically important lipids in predicting the year change in fatigue of subjects with multiple sclerosis. Other papers have identified lysophosphatidylethanolamines (lysoPE) as being a significant lipid signature in patients with MS. Further work must be conducted to investigate the properties of these lipids and determine their biological/physiological significance in the context of multiple sclerosis. However, there is literature that shows that LysoPE 22:5 is significantly decreased in patients with migraines.

#### Electrophysiology and optical coherence tomography of the central retina in aniridia due to PAX6 mutations

Tucker Dangremond<sup>2</sup>, Wanda Pfeifer<sup>1,3</sup>, Megan Helms<sup>3</sup>, Kai Wang, Ph. D<sup>4</sup>, Kyung Moo Lee Ph. D<sup>5</sup>, Arlene Drack, MD<sup>1,2,3</sup>

[1] University of Iowa Department of Ophthalmology & Visual Sciences, [2] University of Iowa Carver College of Medicine [3] Drack Labs, [4] University of Iowa Department of Biostatistics, [5] University of Iowa Institute for Biomedical Imaging

#### Introduction

Patients with aniridia are legally blind from birth and some lose most of their remaining vision over time. Aniridia results from mutations in *PAX6*, a transcription factor gene which plays a crucial role in the normal development of numerous structures, including the eye. Patients with *PAX6* mutations can have a range of ocular malformations including absence or hypoplasia of the iris, macula and fovea of the retina, early development of cataracts and corneal opacity. Early in life hypoplasia of the macula and fovea appears to cause the most vision loss.

#### Purpose

Little work has been done to characterize the structure and electrophysiology of the macula in aniridia patients to determine the role of foveal hypoplasia in vision loss, an important step in developing guided treatment. This study aims to analyze optical coherence tomography (OCT), multifocal electroretinogram (mfERG), and full-field electroretinogram (ffERG) data from aniridia patients and compare to age matched controls.

It was hypothesized that mfERG, which measures electrical activity in the center of the retina at the macula and fovea, would show lower amplitudes in patients with aniridia. It was also hypothesized that ffERG waveforms, which measure the summed electrical activity of the entire retina, would be abnormal. Finally, it was hypothesized that the degree of abnormality measured in electroretinogram studies would correlate with visual acuity and the severity of foveal hypoplasia measured on OCT.

#### Methods

A prospective study and was conducted to obtain mfERG, ffERG, OCT scans and visual acuity measurements in 6 aniridia patients and 18 normal age-similar controls. Amplitude and latency measurements were recorded for each of the six rings on a 61 hexagon mfERG array, as well as for ffERG performed under scotopic 0.01, scotopic 3.0, photopic 3.0 ERG and 30 Hz flicker conditions. Subsequently, nonparametric permutation testing compared amplitude and latency measurements in aniridia patients and controls. Correlation coefficients were calculated to understand the relationship between electrophysiology in the retina, retinal thickness on OCT, and visual acuity.

#### Results

MfERG: Latencies were prolonged in aniridia patients compared to controls. Rings 3-6 had significantly higher amplitudes in aniridia patients than controls (ring 3: p = 0.0152, ring 4: p = 0.0015, ring 5: p = 0.0002, ring 6: p = 0.0008). FfERG: aniridia patients have significantly longer latencies than controls for the photopic 3.0 A wave (p = 0.0141), photopic 3.0 B wave (p = 0.0015), 30 Hz flicker (p = 0.0006), scotopic 3.0 B wave (p = 0.0020), and scotopic 3.0 A wave conditions (p = 0.0011). There was no difference in amplitudes. OCT: A positive correlation was noted between amplitude of mfERG rings 1 & 2 and total retinal thickness on OCT (p = 0.0034, p = 0.0169). Visual acuity: A positive correlation was also noted between visual acuity and scotopic 3.0 B wave amplitude (p = 0.0446). No other correlations with visual acuity were found.

#### **Conclusion/Discussion**

Aniridia patients had higher amplitudes than controls in the outer rings of mfERG, as well as longer latencies. This suggests that the arrangement of electrical activity in the cone and bipolar cells of the retina is abnormal in aniridia patients. Additionally, ffERG testing showed that patients had near normal amplitudes but significantly delayed latencies under most conditions compared to controls. This reveals that *PAX6* mutations don't cause death of the photoreceptors or block their formation, but instead alters their function in some fundamental way.

Identification & Preliminary Characterization of ATF4 Interacting Proteins in Skeletal Muscle Fibers Student: Austin DeLau, M2 Mentor: Chris Adams, MD, PhD, Professor of Medicine Collaborators: Scott Ebert, PhD, Steve Bullard, Jason Dierdorff

**Problem:** Skeletal muscle atrophy diminishes the health and quality of life of tens of millions of people. Causes of muscle atrophy include aging, muscle disuse, malnutrition, critical illness, certain medications and a wide range of chronic illnesses including cancer, heart failure, COPD, diabetes, renal failure, cirrhosis, rheumatoid arthritis, and HIV/AIDS. Despite its broad clinical impact, skeletal muscle atrophy lacks a specific and effective pharmacologic therapy and remains poorly understood at the molecular level.

**Hypothesis:** We hypothesized that skeletal muscle atrophy is caused by a specific transcription regulatory complex within skeletal muscle. When active, this transcription regulatory complex activates specific genes in skeletal muscle (such as the *Gadd45a* and *p21* genes), leading to the expression of signaling proteins that cause muscle atrophy (such as the Gadd45a and p21 proteins). The proteins that comprise this atrophy-promoting transcription regulatory complex are only partly known. At this point, we know that the complex contains the protein ATF4, as well as unidentified proteins that interact with ATF4. To identify those proteins, we biochemically isolated and identified proteins that interact with ATF4 in skeletal muscle fibers in vivo. These ATF4 interactors included five bZIP family members (C/EBP $\alpha$ , C/EBP $\beta$ , C/EBP $\gamma$ , C/EBP $\delta$ , and c-MAF). In this project, we used mouse models to test the hypothesis that C/EBP $\alpha$  and/or C/EBP $\beta$  are required for ATF4-mediated muscle atrophy.

**Methods:** To accomplish this project, we generated and validated RNA interference (RNAi) constructs using a well-established strategy used to knockdown muscle proteins in vivo. Briefly, oligonucleotide duplexes of known sequences targeting the mRNAs of interest (C/EBP $\alpha$  and C/EBP $\beta$ ) were purchased and ligated into the pcDNA6.2GW/EmGFP miR plasmid (Invitrogen), containing a CMV promoter driving co-cistronic expression of engineered RNAi constructs and emGFP. For each targeted mRNA, we developed an RNAi construct that significantly knock down expression of the targeted mRNA in skeletal muscle, as assessed by immunoblot analysis. We transfected these plasmids into healthy young adult (3-mo.-old) mouse TA muscle fibers using electroporation. One TA muscle was co-transfected with plasmid encoding mouse ATF4 + plasmid encoding the RNAi construct of interest, and the contralateral TA, serving as an intrasubject control, were co-transfected with ATF4 plasmid + plasmid encoding the non-targeting control RNAi construct. TA's were harvested 7 days post-transfection for assessment of size of transfected muscle fibers.

#### **Results:**

We generated and validated RNA interference (RNAi) constructs that specifically knock down expression of C/EBP $\alpha$  and C/EBP $\beta$  in vivo, as assed by immunoblot analysis. We transfected these plasmids into mouse TA muscle fibers using electroporation. In fed, fully active, and otherwise healthy young adult (3-mo.-old) mice, one TA muscle was co-transfected with plasmid encoding mouse ATF4 + C/EBP $\alpha$  or C/EBP $\beta$  RNAi construct, and the contralateral TA, serving as an intrasubject control, was co-transfected with ATF4 plasmid + a non-targeting control RNAi construct. We harvested TA's 7 days post-transfection for assessment of transfected muscle fiber size. We found that knockdown of C/EBP $\alpha$  did not decrease ATF4 mediated skeletal muscle atrophy. Interestingly however, knockdown of C/EBP $\beta$  significantly inhibited ATF4's capacity to force muscle atrophy, suggesting that C/EBP $\beta$  is an essential component of the ATF4 transcription regulatory complex that promotes skeletal muscle atrophy.

#### **Discussion:**

In this study, we sought to better understand how ATF4 interacts as a subunit with the heterodimeric bZIP transcription factors C/EBP $\alpha$  and C/EBP $\beta$  in skeletal muscle. We elucidated, via an in vivo knockdown, that the ATF4-C/EBP $\beta$  complex appears to mediate skeletal muscle atrophy and that the ATF4-C/EBP $\alpha$  complex does not. Comprehensive investigations of these ATF4 complexes are still needed and currently underway. Insights from these will build the picture of the upstream mechanism(s) that regulate skeletal muscle atrophy and could serve as important targets for pharmacologic therapy.

### **Obstacles Faced During Bracing in the Treatment of Clubfoot Deformity**

Sarah M. Dougherty, BS<sup>\*</sup>, Victoria L. Troesch, BS<sup>\*</sup>, Thomas Cook, PhD, Qiang An, and Jose A. Morcuende, MD, PhD

# Background

Clubfoot is the most common extremity birth defect. It causes the feet of affected individuals to point inward and downward, which prevents normal walking and leads to a lifetime of disability. Clubfoot can be effectively treated via the Ponseti method, which uses serial casting followed by use of an abduction brace for four years. The brace must be worn according to protocol in order to prevent relapse and ensure full correction of the clubfoot deformity.

#### **Purpose of the Study**

The purpose of this study was to identify what type of braces are most commonly being used by patients with clubfoot, as well as the problems often faced by parents that may negatively impact bracing adherence.

#### Methods

An online-survey was posted on clubfoot support groups for 12 weeks beginning in May, 2018. Parents were asked questions regarding brace characteristics and issues, presence of blisters, as well as if their child had experienced a relapse.

#### Results

There were 982 responses to the survey. 50.60% of children use the MD Orthopedics/Ponseti boots, while 14.15% of children use the ADM brace. Over half of the respondents (52.38%) stated that their child has had skin irritations and/or blisters. Children whose parents reported that they wore thick socks were 1.55 times more likely to have blisters than children whose parents reported that they wore thin socks (p=0.0220). 15% of parents reported that their child experienced a relapse during their course of treatment. Less than half of parents (46%) were told to wear the brace for the standard 4-years. Parents whose children did not experience a relapse were 1.83 times more likely to report their child's comfort level to be high than parents of children who did experience a recurrence (p=0.0052). In addition, parents who reported their child experiencing a relapse were 1.748 times more likely to also report that their child's foot has slipped out one or more times (p=0.0316).

#### Conclusions

Physicians and parents should be aware of common obstacles to bracing adherence, so that these challenges can be anticipated and accounted for. In additions, parents should be informed about the benefits of certain brace types. Better education and patient-centered care will allow for a more manageable bracing period and more successful outcomes.

# Assessing balance and determining assistive device use in older adults in community settings using a mobile health platform

Nicholas Evans, Philip Polgreen

**Background:** Falls among older adults are a major cause of morbidity and mortality. Falls often cause disabling fractures and/or head injuries leading to further disability. Thus, preventing falls is a major public health priority. An important component of fall prevention is risk detection. Most previous work is survey-based and relies on self-report. Equipment to assess balance exists, however in many cases the cost to use such equipment is prohibitive. Recently, less expensive approaches have been developed. While some approaches (e.g., using force platforms or Wii Balance Boards) have been validated and compare favorably to alternative fall prevention measures, they have relied upon custom software that is not generally available in hospital or ambulatory care settings and are difficult to use by non-technical personnel.

**Purpose:** The purpose of this project is two-fold: 1) to update a platform we developed last summer for rapidly detecting deficiencies in balance, and 2) to use this system to assess the balance of older adults and predict their use of an assistive device (e.g., a walker or cane).

**Methods:** We designed and implemented custom software to collect data via Bluetooth from the force sensors from a Wii Balance Board (WiiBB), an inexpensive controller associated with the popular Nintendo Wii game console. Following a usability study conducted last summer, the software was updated to be easier to use and more robust for use by non-research personnel. For this study, participants first completed a modified Vulnerable Elders Survey. They were then asked to complete a series of 4 tests on a WiiBB for 30 seconds each: (1) eyes open, feet apart; (2) eyes open, feet together; (3) eyes closed, feet apart; and (4) eyes closed, feet together. The order of the tasks was randomly chosen by the software for each subject. The subject was then asked to repeat the four tasks. The raw force sensor data for each trial was timestamped and saved with the subject identifier for later analysis. The sample rate for each sensor varied between 30 and 100 Hz (i.e., samples recorded per second).

**Results:** 109 subjects completed the study. Based on the raw data from these subjects that we have enrolled to date, we have developed several features (e.g., anteroposterior and mediolateral maximum displacement, average speed of displacement) that capture the amplitude and duration of the deviations from the balanced state. We used standard machine learning approaches to predict whether a subject uses a gait-stabilizing (assistive) device based on the extracted features. Our preliminary results indicate that when five-fold cross-validation is used, we were able to achieve promising results (AUC of 0.76) for predicting use of a gait-stabilizing device.

**Conclusions:** Because of the affordability of our platform (requiring only a \$40 Wii Balance board and Bluetooth-capable laptop or tablet), it can easily be scaled for use in both research, and ultimately, clinical practice for safety and quality fall-prevention initiatives. We will continue to gather data to improve the performance of our classifier.

#### A Retrospective Review of Percutaneous Ultrasonic Tenotomy for Chronic Tendinopathies

Ben Fick; Daniel Stover; Andrew Peterson, MD; Ruth Chimenti, DPT, PhD; Mederic Hall, MD

#### Background

Historically, tendinopathy treatment has focused on rehabilitative exercises, and rarely surgery. Now, new methods of treatment are being explored such as: Tendon scraping, Percutaneous needle tenotomy, Percutaneous ultrasonic tenotomy (PUT), and Platelet rich plasma injection (PRP). PUT removes neovascularization and scar tissue within the tendon. The effectiveness of PUT performed with TENEX TX devices was analyzed in this study. As this is a new treatment, it is vital to establish safety and efficacy data to inform evidence based clinical decisions and as a means for continuous improvements in patient care.

#### Purpose

The aim of this study is to determine the overall effectiveness of PUT by analyzing pain, function, and complications, before and after each procedure.

Hypothesis: There is an improvement in pain and function between pre-treatment baseline, short-term follow-up (2, 6, or 12 weeks), and/or long-term follow-up of PUT performed with TENEX with a low risk of complications.

#### Methods

A retrospective review of 285 patients was conducted by analyzing pain, function, and complications related to PUT. Multiple sites were analyzed including patellar (n=41), midportion achilles (n=26), insertional achilles (n = 34), plantar fascia (n=87), and elbow (n = 97). The outcomes were determined at baseline, short-term follow-up (6 week, or 12 week), and long-term follow-up. Outcomes at short-term follow-up were collected by chart review, while long-term outcomes were supplemented by additional email or telephone follow-up. Wilcoxon Signed Rank tests were used to compare pain on a 4-point scale between baseline, short-term, and long-term follow-up. Paired t-tests were used to compare SF-12 Physical Component Summary (PCS) scores between baseline, short-term, and long-term follow-up. Demographics and complications were also evaluated for association with the procedure.

#### <u>Results</u>

The groups were demographically homogenous with mean age ranging from 49.9 to 53.7 years old, mean BMI from 28.8 to 30.8 kg/m<sup>2</sup>, and race ranging from 89% - 94% Caucasian. The exception to this included the patellar group as the mean age was 30 years old, mean BMI was 26 kg/m<sup>2</sup> and race was 79% Caucasian. Response rate at long-term follow-up was highest for the Achilles and Plantar fascia sites (74%) and lowest for those patellar pain (58%). Pain improved significantly in each group at short-term and long-term follow-up (p<0.05; Table 1).

Table 1.	Tendinopathy Pain Site (% Response Rate)									
	Patellar (58%)		Achilles –		Achilles –		Plantar Fascia		Elbow (62%)	
			Midportion (74%)		Insertional (61%)		(74%)			
	Moderate	None	Moderate	None	Moderate	None	Moderate	None	Moderate	None
	to Severe	to	to Severe	to	to Severe	to	to Severe	to	to Severe	to
		Slight		Slight		Slight		Slight		Slight
Baseline	62%	38%	82%	18%	78%	12%	95%	5%	91%	9%
Short-	Not reported		Not reported		37%	63%	45%	55%	25%	75%
term										
Long-	15%	85%	6%	94%	14%	86%	21%	79%	8%	92%
term										

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Table 2.	Tendinopathy Site – SF12 PCS								
	Patellar	Achilles –	Achilles –	Plantar Fascia	Elbow				
		Midportion	Insertional						
Baseline	41.7	36.8	40.8	36.0	36.7				
Short-term	Not Reported	Not Reported	44.0	40.1	41.7				
Long-term	49.2	49.2	Not Reported	48.0	48.0				

Complications were limited at each site with only one non-infectious wound complication, four cases of increased pain post-procedure, and one case of hypersensitivity post-procedure.

#### Discussion

The efficacy and safety of PUT was analyzed in this study. PUT can decrease pain and improve overall physical health both in the short-term and long-term while maintaining a low complication rate. Further research should be conducted in the future to verify these results.

# MRI Occult Meniscal Tears of the ACL Deficient Knee: Characterization of Occult Meniscal Tears and Association with Medial Femoral Condyle Rim Bone Contusions

Nick Fleege, D. Lee Bennett MD, Howard O'Rourke MD, Kenjirou Ohashi MD

Department of Radiology, UIHC

**PURPOSE:** Identifying meniscal tears by MRI, specifically lateral meniscal tears, has a largerthan-expected error rate in the presence of an anterior cruciate ligament (ACL) tear. The purpose of our study was to search for a bone contusion that is associated with occult meniscal tears with a concomitant ACL tear, specifically a contusion of the rim of the medial femoral condyle (RMFC). We also categorized the type, size, and location of these occult meniscal tears, and the sex of the patients with these tears.

**MATERIALS AND METHODS:** This was a retrospective study that examined characteristics of occult meniscal tears and their association with a RMFC contusion. Institutional Review Board (IRB) approval was obtained. The date range of the study was from June 2009 through December 2015. A total of 6,392 knee MRI reports were reviewed. The study group included 22 patients; the control group included 110 patients. Relevant statistical values were calculated.

**RESULTS:** The most common type of occult meniscal tears were small radial and small longitudinal tears of the posterior horn of the lateral meniscus. Occult meniscal tears were associated with RMFC contusions in the study group (P=0.0457), particularly in males (P=0.0003). In males with a torn ACL, the sensitivity of an RMFC contusion for an occult meniscal tear was 80%.

**CONCLUSION:** In males with an ACL tear, there was a significant association between a contusion of the RMFC and an occult meniscal tear (commonly small radial or peripheral tears). RMFC contusions were reliably identified by radiologists in this study.

# Implementation of an ED mechanical ventilation protocol improves compliance with lung protective ventilation

Tyler Foley, BS<sup>1</sup>; Brittany Philpot, MD<sup>2</sup>; Alysa Davis, DO<sup>2</sup>; Karisa Harland, PhD, MPH<sup>2</sup>; Brian M. Fuller, MD, MSCI<sup>3</sup>; Nicholas Mohr, MD, MS<sup>4</sup>

<sup>1</sup>University of Iowa Carver College of Medicine, Iowa City, IA <sup>2</sup>Department of Emergency Medicine, University of Iowa Carver College of Medicine, Iowa City, IA <sup>3</sup>Departments of Emergency Medicine and Anesthesiology, Division of Critical Care, Washington University School of Medicine, St Louis, MO

<sup>4</sup>Departments of Emergency Medicine and Anesthesiology, Division of Critical Care, University of Iowa Carver College of Medicine, Iowa City, IA

**Background:** Utilization of lung-protective mechanical ventilation in the emergency department (ED) has been shown to reduce hospital mortality and pulmonary complications such as acute respiratory distress syndrome. The objective of this study was to determine the impact of a mechanical ventilation protocol implemented in our ED on adherence to lung-protective ventilation and subsequent clinical outcomes.

**Methods:** This study was a retrospective, before-after cohort study (March 2016 to July 2018) of mechanically ventilated patients in an academic 60,000-visit ED, 15 months before through 13 months after the implementation of a lung-protective ventilation protocol. This multifaceted protocol was implemented by respiratory therapists and included parameters for low tidal volume (<8 mL/kg predicted body weight), PEEP (using PEEP table and additional obesity parameters), FiO<sub>2</sub>, and respiratory rate. Patients were divided into pre- and post-protocol groups, and initial ventilator settings in the ED and ICU were collected, along with clinical outcomes. The primary outcome of this study was mean difference in tidal volume administered in the ED between groups, and the study was powered to detect a difference of 0.3 mL/kg. Secondary outcomes included protocol adherence, ventilator-free days, and mortality.

**Results:** A total of 501 cases (272 pre-protocol, 229 post-protocol) were included. A mean tidal volume of 6.7 mL/kg was used pre-protocol compared to 6.3 mL/kg post-protocol, for a mean decrease of 0.35 mL/kg (p=0.001). Between the pre-protocol and post-protocol groups, adherence to the tidal volume target increased from 88.0% to 94.3% (p=0.020), FiO<sub>2</sub> adherence increased from 23.2% to 34.1% (p=0.007), PEEP adherence increased from 15.7% to 28.0% (p=0.004), and respiratory rate adherence increased from 74.6% to 85.2% (0.0037). There was no significant difference in hospital mortality (24% vs. 25%, p=0.83) or 28-day ventilator-free days (19.7 vs. 19.3 days, p=0.76) between the two groups.

**Conclusion:** Implementation of an ED-based lung-protective ventilation protocol is associated with increased adherence to all ventilator parameters, including decreased tidal volume, hyperoxia, and hyperventilation, as well as more appropriate PEEP setting.

#### Pediatric Surgery Near the End of Life

Julia Gales, BS, Erica Carlisle, MD, Dr. Shilyansky, MD

**Introduction**: Literature exists showing that adults rely upon costly, resource-intensive health care during their final year of life. While several studies investigate the health care resources children use near the end of life, there is currently no data on the surgical procedures that children undergo in their final year of life. This data is essential in framing discussions with families caring for these children and may also help providers determine which procedures may not be helpful in prolonging a child's life. Data was gathered about health care utilization, specifically about procedures and surgeries performed, using charts from patients under 18 who died while being cared for at University of Iowa Hospitals and Clinics (UIHC).

#### Aims:

- 1. Identify the surgeries and procedures performed in children during their last year of life and terminal admission.
- 2. Use the variables identified to examine outcomes related to surgery including number and duration of hospitalizations.

**Methods:** The study was a retrospective chart review of all patients under the age of 18 who have died from 2013-2017 while being cared for by providers at UIHC. The following data was abstracted from each patient's chart: diagnosis, cause of death, date of death, number of hospitalizations in the last year of life, duration of each hospitalization, inpatient or outpatient status at the time of death, number and type of surgeries and procedures during the terminal hospitalization, number and type of surgeries and procedures during the final year of life, age at death, gestational age, gender, race, and ethnicity. These results were compared across diagnosis.

**Results:** 526 children cared for at UIHC in their final year of life died from 2013-2017. 64% of these children died while admitted to the hospital. Children with cardiac diagnoses, trauma, and preterm/birth complications were more likely to die while admitted to the hospital. Children with neurologic conditions were more likely to die outside the hospital, while those with genetic and oncologic conditions were almost equally likely to die while admitted to or outside the hospital. Children had an average of  $1.7\pm 2.6$  hospitalizations, and they had an average of  $1\pm 1.8$  surgeries and  $1.25\pm 2.8$  procedures in their final year of life. Of the children who died while admitted to the hospital, there was an average of  $1\pm 1.8$  surgeries and  $1.25\pm 2.3$  procedures performed during their terminal hospitalization. The most frequent types of surgeries performed included abdominal (89), cardiac/ECMO (117/42), ENT (67), neurologic (71), and thoracic (36). The most frequent procedures performed included venous access (341), intubation (48), bone marrow biopsy (48), chest tube placement (52), endoscopy (38), and thoracentesis (39).

**Conclusions:** As seen in adults, children are more likely to die in the hospital than outside it, even though their disease burden differs demographically. When dividing children amongst their diagnoses, patterns emerge regarding the type and number of procedures and surgeries performed. Further analysis on this type of data could help inform pediatric surgeons of which operations may be potentially futile to patients.

# Identification of biomic variables impacting clinical outcomes in non-small cell lung cancer patients to improve imaged-based machine learning response prediction

Mentor: Dr. Yusung Kim Collaborators: Yusen He, Katherine Cabel, Dr. Brian Smith

Automated machine learning (ML) based tools with the capacity to predict clinical outcomes offer a promising future for individualized medicine, particularly for cancer therapeutic decision making. Current ML models make use of either "radiomic" tumor CT image data or "biomic" clinical/genomic data to predict patient outcomes before cancer treatment. It is of great interest to develop a ML tool which would utilize both factors-a patient's radiomic and biomic data-to predict some measure of clinical outcome. However, even within the discrete set of diseases classified as non-small cell lung cancers (NSCLCs) biomic factors impacting clinical outcomes vary from study to study. Furthermore, it is unclear which clinical outcome metrics are reproducibly predictable and ultimately practical for physician use in deciding course of treatment. In this study we aimed to (1) determine clinical outcome metrics which are both feasible and practical to predict and (2) determine what clinical factors, or "predictors" significantly impact these clinical outcomes. The data set, which was also used for training our current radiomic-based ML tool, included 116 patients with NSCLC treated with stereotactic body radiotherapy (SBRT). Patient clinical outcomes of disease free survival (DFS) and overall survival (OS) as well as a vast number of biomic predictors such as smoking pack years, stage, and KPS score were extracted and recorded from patient records. Both DFS and OS were used as outcome metrics and analyzed with multivariate Cox regression. Predictors included in the regression analysis were identified using AIC-based stepwise variable selection. 5 biomic variables were identified for inclusion in the OS model (prior surgical resection, prior radiation treatment, previous cancer diagnosis, age, and stage) and 2 biomic variables were identified for inclusion in the DFS model (prior radiation therapy, KPS score). Concordance indices (c-statistics) were found to be 0.66 and 0.59 for OS and DFS models, respectively. Given these results, we hypothesize that incorporation of the identified biomic variables will result in a biomic/radiomic-based ML tool with superior predictive power as compared to our current radiomics-based ML tool. Integration of these biomic predictors into our current ML algorithm is currently underway.

# **Deep Sedation is Associated with Increased Mortality in Mechanically Ventilated Air Transport Patients: A Cohort Study**

Brendan P. George, BA<sup>1</sup>; Nicholas M. Mohr, MD, MS<sup>1,2,3</sup>; J. Priyanka Vakkalanka, ScM<sup>1,2</sup>; Karisa K. Harland, MPH, PhD<sup>1,2</sup>; Brian M. Fuller, MD, MSCI<sup>4,5</sup>; Azeemuddin Ahmed, MD, MBA<sup>1</sup>

<sup>1</sup> Department of Emergency Medicine, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA

<sup>2</sup> Department of Epidemiology, University of Iowa College of Public Health, Iowa City, Iowa, USA

<sup>3</sup> Department of Anesthesia, Division of Critical Care, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA

4 Department of Anesthesiology, Division of Critical Care, Washington University School of Medicine in St. Louis, St. Louis, Missouri, USA

<sup>5</sup> Department of Emergency Medicine, Washington University School of Medicine in St. Louis, St. Louis, Missouri, USA

# Background

Intubated patients with acute respiratory failure are commonly transported by air ambulance and require sedation for mechanical ventilation. Prior work has shown that depth of sedation influences ventilation duration, delirium, and survival among critically ill adults. These relationships have not been tested in the prehospital environment. The primary objective of this study is to measure the relationship between air ambulance sedation during transfer and patient outcomes.

# Methods

A retrospective cohort study of mechanically ventilated patients transferred by air ambulance to a single 812-bed Midwestern academic medical center from July 2013 to May 2018. Prehospital sedation medications and depth of sedation [Richmond Agitation-Sedation Scale score (RASS)] were investigated. Primary outcome was delirium. Secondary outcomes were lengths of hospital stay and mechanical ventilation, in-hospital mortality, and need for neurosurgical procedures. Univariate analyses were used to measure the association between sedatives (and drug combinations) and clinical outcomes. Multivariable models adjusted for potentially confounding covariates to measure the impact of predictors on delirium and mortality.

# Results

Three hundred twenty-seven patients were included. Amongst those patients, 156 (47.7%) received benzodiazepines, 155 (47.4%) received opiates, 90 (27.5%) received long-acting paralytics, 77 (23.5%) received propofol, and 25 (7.6%) received ketamine. No association existed between any medication and development of delirium. Benzodiazepines were associated with a mean increase of 2.9 days in the hospital (95% CI, 0.7-5.1). In multivariable modeling, for every one-unit increase in prehospital RASS score (e.g. -4 to -3), there was a 24% decrease in odds of death (OR, 0.76; 95% CI, 0.65-0.90); for every one-unit increase in emergency department (ED) RASS score, there was a 43% decrease in odds of death (OR, 0.57; 95% CI, 0.41-0.79). Delirium was not associated with prehospital or ED RASS scores.

# Conclusions

Benzodiazepines were the most commonly administered prehospital sedative and are associated with increased hospital length-of-stay. Deep sedation in both the prehospital and ED settings was associated with increased mortality. Sedative administration during air transport is a modifiable risk factor and requires prospective study.

Quantitative Susceptibility Mapping (QSM) and Vessel Wall Imaging (VWI) MRI Sequences in Identifying Subjects with Intracranial Aneurysms who Have Microbleeds Associated with Sentinel Headache: Pilot Study

Mentor: Dr. David Hasan M2: Shadeh Ghaffari-Rafi

# ABSTRACT

# **Background and Purpose:**

Sentinel headache (SH) associated with cerebral aneurysms (CAs) significantly increases the risk of rupture. Distinguishing SH from common variety headaches can be challenging occasionally. Here we propose a novel treatment guideline based on MRI protocol that could enable physicians to objectively diagnose microbleeds associated with SH.

# **Methods:**

Twenty-eight consecutive subjects with a total of 35 CAs were enrolled in this pilot study during a period from March 2018 to July 2018. All subjects presented to with different types of headaches. All subjects were evaluated with new MRI protocols which included: MRA with Gadolinium, high-resolution magnetic resonance vessel wall imaging (MR-VWI) and MR imaging quantitative susceptibility mapping (MRI-QSM) scanning using 3T MRI machine.

# **Results:**

All 35 CAs (100%) visualized on MR-VWI, whereas MRI-QSM was able to visualize only 24 CAs (77.1%) due to MRI artifact generated by proximity to skull base bone (P=0.005). Fifty percent (50%) of anterior communicating artery aneurysm were not visualized on MRI-QSM map. Four subjects presented with typical discerption of SH. All of 4 of these subjects had negative head CT and lumbar puncture. Microbleeds detected on MRI-QSM was seen in all of these 4 subjects who underwent urgent treatment. The histological report indicated that signal intensity in MR-VWI corresponded to the enhancement correlates with the thickness of the aneurysm wall. The thicker the aneurysm wall, the more avid the enhancement. This enhancement noted to be due to thick atherosclerotic layer and/or neointimal layer.

# **Conclusions:**

Our study suggested that our proposed treatment paradigm may be useful as an adjunctive guide to discriminate unstable aneurysms from stable ones.

#### The Effect of Eyelid Surgery on the Ocular Surface, Tear Composition, and Meibomian Gland Morphology and Function

Pavane L. Gorrepati, BA<sup>1</sup>, Audrey C. Ko, MD<sup>2</sup>, Christine Sindt, OD, FAAO<sup>2</sup>, Keith Carter, MD, FACS<sup>2</sup>, Erin Shriver, MD, FACS<sup>2</sup>

<sup>1</sup>Carver College of Medicine, University of Iowa, 375 Newton Road, Iowa City, Iowa 52242, USA <sup>2</sup>Department of Ophthalmology and Visual Sciences, University of Iowa, 200 Hawkins Drive, Iowa City, IA, 52242, USA

**Background:** It is known that eyelid surgery directly affects blink dynamics and meibomian glands, but little is known regarding the effect of eyelid surgery on dry eye markers, tear film composition, and meibomian gland morphology. To date, the most studied eyelid surgery is upper eyelid blepharoplasty, which has been demonstrated to result in dry eye symptoms in 11-27% of patients post-operatively.<sup>1</sup> The incidence of dry eye is greater in patients who undergo concurrent upper and lower eyelid surgery and those who undergo resection of the orbicularis muscle in addition to skin resection.<sup>2</sup> While dry eye symptoms post blepharoplasty are established, the literature is lacking on the procedure's effect on objective measures of dry eye such as tear meniscus and meibomian gland morphology.

**Purpose of Study:** This study aimed to determine the effect of various eyelid procedures on meibomian gland morphology, tear composition, and dry eye symptoms. It was postulated that eyelid procedures not directly affecting the orbicularis oculi muscles or the tarsal plates would cause short term changes in these measures due to inflammation and decreased blinking secondary to edema. Additionally, it was hypothesized that patients will return to their preoperative levels by postoperative month 2. In procedures where the tarsal plate is incised/excised, it was postulated that there will be significantly more meibomian gland atrophy and dry eye symptoms long-term.

**Methods:** A prospective study evaluating all patients undergoing elective eyelid procedures with the University of Iowa Oculoplastics Division was conducted in compliance with the Institutional Review Board. The procedures include blepharoplasty, ptosis repair, ectropion repair, eyelid reconstruction after Mohs excision of malignancy, etc. Preoperative and postoperative measurements of tear meniscus, imaging of Meibomian glands, and ocular redness were collected using the Oculus Keratograph 5M. A subjective dry eye score using the Ocular Surface Disease Index (OSDI) was also collected. All patients were evaluated preoperatively and at one-week postoperatively and will be evaluated at 2 months and 6 months postoperatively.

**Results:** To date, 17 patients were included in this analysis of patients preoperatively and one-week postoperatively. Patients underwent bilateral upper lid blepharoplasty, bilateral lower lid lateral tarsal strip, and bilateral ptosis repair. No significant differences were noted in all patients between the preoperative and one-week postoperative OSDI scores and OSDI dry eye categorization. There were no significant differences noted between preoperative and one-week postoperative tear meniscus height in the right eye, but there was a significant increase in the left eye tear meniscus height. There was a significant increase in the right eye temporal bulbar redness, nasal bulbar redness, temporal limbal redness, and bulbar redness measurements.

**Conclusion/Discussion:** These findings suggest that eyelid surgery does not significantly impact subjective dry eye conditions at one-week postoperatively. There is a significant increase in ocular redness in the right eye and tear meniscus height in the left eye at one-week postoperatively, despite all procedures being bilateral. Future directions include continuing to recruit patients and following up with patients at 2 months and 6 months postoperatively. With a greater sample size, significant differences in redness measurements and tear meniscus height may present bilaterally or may prove insignificant. At 2 months postoperatively, measures will be reassessed and meibomian gland images will be taken and compared to images taken preoperatively to determine if any meibomian gland dropout has occurred.

<sup>1.</sup> Prischmann J1, Sufyan A, Ting JY, Ruffin C, Perkins SW. Dry eye symptoms and chemosis following blepharoplasty: a 10year retrospective review of 892 cases in a single-surgeon series. *AMA Facial Plast Surg.* 2013 Jan;15(1):39-46. doi: 10.1001/2013.jamafacial.1.

<sup>2.</sup> Terella AM1, Wang TD, Kim MM. Complications in periorbital surgery. *Facial Plast Surg.* 2013 Feb;29(1):64-70. doi: 10.1055/s-0033-1333838. Epub 2013 Feb 20.
## Student: Brian Grieve Supervisor: Dr. Lucy Wibbenmeyer

## Introduction:

BWC continues to be one of the most prevalent infectious complications in burn wound treatment, second only to pneumonia and UTI. The aim of this study was to validate results from a retrospective study performed at our institution. A further aim was to delineate the relationship between initial burn first aid and delays in medical care on development of BWC.

## Methods:

Subjects were recruited from UIHC Burn Treatment Center (BTC) from June 2014 – June 2018. All thermal burn injury patients admitted for >24 hours were approached for consent. Patients were excluded if they (1) received antibiotic treatment within 10 days prior to burn injury, (2) received antibiotic treatment within three days post-injury for any other reason than BWC.

## **<u>Results:</u>** $(p = \langle 0.05 \rangle * Multi-variable analysis is currently underway.$

**Demographics -** 286 subjects met inclusion criteria for data analysis and 77 were excluded. 92 (32%) of the study group developed BWC. The remaining 194 (68%) subjects served as controls. The BWC group was significantly older, had a higher BMI and had fewer multi-racial or African American subjects.

At Home Care - The BWC group less often used water from the bath tub or shower, and more often from a sink. The BWC group more often rolled on "other" surfaces to extinguish flames. The BWC group more often attempted to clean their burn before seeking care and used only water to do so. BWC patients more often placed something onto their burn, more often being an antibacterial. Fewer BWC patients went to an OSH ER as the 1st professional care sought. Significantly fewer sought any care within 3 hours of their injury; and more waited  $\geq$ 72 hours. Fewer BWC patients were admitted to UIHC BTC, or received any form of professional care within 24 hours of injury.

**Injury Location -** BWC appears to be more closely associated with sustaining an injury to the feet or lower extremities. No significant difference is seen in upper extremity or torso burns; and sustaining a burn to the hands or the head/neck appears to be relatively protective.

## Injury Characteristics (FT: full-thickness, PT: partial-thickness)

BWC group had smaller total %TBSA burns. More BWC patients sustained entirely FT burns and among those patients with mixed depth burns, the BWC group had greater FT areas. Lower extremities were the only anatomic location with significant differences in TBSA and burn depth. Among those who sustained LE burns, the BWC group had larger areas of FT burn and a greater proportion had any presences of FT burn. The BWC group had significantly more contact burns and no electrical burns.

## **Hospital Stay**

BWC group had a longer time from injury to admission, and injury to surgery. BWC had 1.59 times as more hospital charges / %TBSA burned despite having smaller burns and a similar inpatient LOS. This is reflected by the greater proportion of BWC patients who required surgery within 10 days of their injury; required antibiotic therapy (not including for surgical prophylaxis) and required opioids. The BWC group received more IV Dilaudid and IV Ancef. BWC patients also more often required a 2<sup>nd</sup> unplanned admission.

## Wound cultures

BWC sites had a greater number of species per wound culture, as well as a higher prevalence of Group-A Strep.

## Comorbidities

A greater proportion of the BWC group had at least one comorbidity, a greater number of total comorbidities. BWC had more obesity, more current tobacco users, more diabetes mellitus, more hypertension and history of pulmonary embolism. Fewer BWC patients had a UDS test done at UIHC; however more often had positive results. These were more often positive for methamphetamine or cocaine.

## **Conclusion:**

Almost three quarters of patients who developed BWC were in our care in some capacity at the time of infection. Those who presented with BWC had a significantly longer treatment delay and performed first-aid prior to seeking professional care that may have been deleterious. Both BWC groups had a significantly greater number of days between injury and surgical intervention. Lastly, this study supports several risk factors found retrospectively. Education reinforcement in the community on proper initial burn wound care and early treatment from an Emergency Department or Burn Center may lower BWC rates, and the sequelae and healthcare costs that accompany it. The results may suggest the utility of supplemental resources for providers to encourage considering earlier transfer, earlier admission and earlier surgical intervention to prevent BWC development in patients who meet certain risk factors for developing BWC. However, further dataset analysis is needed before any concrete suggestions may be made.

## Relationships between symptoms, patient demographics, and cervical cancer

Hayley Hansen, M2 Dr. Colleen Stockdale, MD, MS, Dr. Abbey Hardy-Fairbanks, MD Dr. Colette Gnade, MD, PGY-2 Kelsey Sheets, M3

#### Background

Timely detection and treatment of cervical cancer is important for maximizing patient survival. While cervical cancer screening has significantly reduced mortality and morbidity in the United States and Iowa, screening remains opportunistic. Delays in diagnoses and subsequent treatments due to this phenomenon can have significant consequences for patient outcomes.

### Aim

Our aim for this preliminary sub-analysis was to identify potential associations between the presence of symptoms and patient demographics among women with a diagnosis of cervical cancer at an academic referral center.

### Methods

A retrospective study of UIHC chart data collected between January 1, 1986 and September 6, 2017 was performed. This included data from Epic, Care Everywhere, and paper charts. The variables studied were: presentation at diagnosis, age, race, BMI, smoking status, FIGO stage at diagnosis, history of other cancer within 5 years of cervical cancer diagnosis, history of immunodeficiency, and cervical cancer screening timeline (pap timeline). Presentation at diagnosis of cervical cancer included: (1) screening pap/colposcopy, (2) symptoms, (3) asymptomatic with pelvic exam, and (4) unknown. Values 1, 3, and 4 were combined and given the designation of 1, representing No Symptoms (n=234). Value 2 remained unchanged, representing Symptoms (n=431). Chi-square tests and t-tests were performed with 95% confidence intervals (CI) to analyze categorical and continuous variables, respectively.

## Results

Six-hundred and sixty-five (665) patients were analyzed, 431 symptomatic and 234 asymptomatic at cervical cancer diagnosis. Women, ages  $\geq$ 41 (71.0%), were more likely than their younger cohorts, ages  $\leq$ 40 (29.0%), to be symptomatic at the time of their diagnosis. This finding was further reflected in the mean age at diagnosis for symptomatic women, 49.31(±14.09) years, versus asymptomatic women, 42.15(±13.01) years (p<0.001). Regarding advanced FIGO stage at diagnosis ( $\geq$ IIIA, n=104), women were more likely to be symptomatic (n=98) than asymptomatic (n=6; p=0.54). Out of two-hundred and fifty-eight (258) women who correctly followed screening guidelines, having at least one pap in a 5-year period for women  $\leq$ 65 years old or a negative pap within 5 years of screen-out at age 65, 143 were symptomatic and 115 were asymptomatic at cervical cancer diagnosis (p=0.02). In comparison, 246 women did not follow correct screening guidelines, 191 symptomatic and 55 asymptomatic (p=0.77).

## Conclusion

From our analysis, women ages  $\geq$ 41 are more likely to present with symptoms at diagnosis of cervical cancer in comparison to their younger counterparts. This is consistent with the average age of early cervical cancer diagnosis of 42 years in the U.S. and the finding that women with cervical cancer diagnosis at an earlier age are more likely to be identified via routine screening.

Interestingly, the association between advanced FIGO stage at diagnosis and symptomatic presentation was not statistically significant (p=0.54), although more women with an advanced FIGO stage were symptomatic at diagnosis (n=98). It is possible that the study's sample size was too small to measure an association between these variables, as one would reasonably conclude that women with more advanced cervical cancer would be more likely to show symptoms than those with early invasion.

Another point of interest is the association between correct versus incorrect screening and symptoms. Although women at our institution were more likely to be symptomatic at diagnosis regardless of adherence to proper screening, 44.6% of women who correctly followed screening guidelines were asymptomatic at diagnosis. In comparison, 22.4% of women who did not follow screening guidelines were asymptomatic. The importance of compliance with pap screening in the prevention of disease progression and mortality is demonstrated here. Almost twice as many women in the correct screening group versus the incorrect screening group had their cervical cancer detected before it advanced to symptomatic presentation. Thus, encouraging women to obtain recommended screening, especially those within the 41–60 age group, is of significant importance.

Human Pseudoislets as a 3D Model to Address the Regulation of Insulin Secretion

Mikako Harata, Siming Liu, Joseph Promes, James Ankrum, and Yumi Imai

Insulin secretion impairment is a key pathological indicator of type 2 diabetes that manifests in the early stages of disease progression. It is recognized that the three-dimensional structure of pancreatic islets plays a key role in robust insulin secretion. In an attempt to develop a model to study the regulation of insulin secretion in human islets that show prominent first phase of insulin secretion, we created reaggregated human pancreatic islets (pseudoislets). In contrast to conventional non-reaggregated islets, pseudoislets maintained high functionality for up to 3 weeks of culture with better preservation of first phase response to glucose. Pseudoislets also maintained insulin secretion to KCl, arginine and glibenclamide compared to non-dispersed cultured islets. Gene expression data indicated that pseudoislets contains all types of endocrine cells originally present in islets. The expression of beta cell maturation markers and type 1 collagen were increased in pseudoislets compared to fresh islets, while the expression of inflammatory genes were reduced. We then tested the feasibility of the lentivirus mediated genetic modification of human pseudoislets with GFP as a positive indicator and noted that lentivirus efficiently transduce pseudoislets without impairing insulin secretion. We also introduced short hairpin RNA lentiviral vector constructs to downregulate glucokinase (GcK) and achieved significant reduction of GcK. In summary, human pseudoislets provide a novel approach for investigating a molecular basis of GSIS under physiologically relevant condition by allowing the better preservation of insulin secretion and genetic modulation of human islets.

## Prediction Model for Diagnosing Patients with Anaphylaxis in the Emergency Department

Cassandra Hardy, B.S.<sup>1</sup>; Karisa Harland, PhD, MPH<sup>2</sup>; Ronna L Campbell, MD, PhD<sup>3</sup>; Zuhair K. Ballas, MD<sup>4</sup>; and Sangil Lee, MD, MS<sup>2</sup>

<sup>1</sup>Carver College of Medicine, University of Iowa, Iowa City, IA

<sup>2</sup>Department of Emergency Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA

<sup>3</sup>Department of Emergency Medicine, Mayo Clinic, Rochester, MN

<sup>4</sup>Division of Immunology, University of Iowa Carver College of Medicine, and the Iowa City VA Iowa City, IA

#### Background

Anaphylaxis is a common condition treated in the ED and outpatient clinics with the severity of symptoms varying. The National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network (NIAID/FAAN) has developed criteria to help diagnose anaphylaxis, but the criteria are somewhat cumbersome to use in an emergency setting. It is less likely that allied health professionals and community healthcare workers can use the criteria to identify anaphylaxis. The objective is to develop an algorithm so that healthcare providers can quickly and accurately calculate the likelihood that a patient has anaphylaxis.

#### Methods

A prospective study was conducted using convenient sampling of patients presenting to the ED from June 2017 to July 2018 with chief complaints of allergic reactions, food allergy, insect or wasp stings, medication reaction, angioedema, or anaphylaxis. Data were collected on patient demographics, inciting allergen, time of onset, signs and symptoms, medications, ED management, disposition, and follow-up. Authors conducted logistic regression to measure the association between exposure to inciting trigger, time of onset, clinical signs and symptoms and anaphylaxis criteria meeting NIAID/FAAN criteria. Lastly, we selected the prediction model based on c-statistics and the simplicity.

#### Results

A total of 141 patients were included with a median age of 27 years (IQR, 18-48 years) and 79 (56%) patients were female. Sixty-eight (48%) of the patients met NIAID/FAAN criteria for anaphylaxis. The provider did not diagnose the patient with anaphylaxis when they met NIAID/FAAN criteria in 33 cases (false negative), and the provider diagnosed anaphylaxis when the patient did not meet NIAID/FAAN criteria in 3 cases (false positive). Logistic regression demonstrated that the combination of food allergy (OR 3.67; 95%CI 1.37-10.5), angioedema (OR 4.98; 95%CI 1.81-15.4), shortness of breath (OR 20.3; 95%CI 5.62-103), nausea (OR 10.9; 95%CI 2.80-49.8), and voice change (OR51.1; 95%CI 8.99-978), were associated with meeting NIAID/FAAN criteria, with its c-statistic of 0.9.

#### Conclusion

The NIAID/FAAN criteria for anaphylaxis can be difficult to use in emergencies resulting in the underdiagnosis of anaphylaxis. After the validation, our simple prediction model may help healthcare providers to recognize anaphylaxis more accurately.

## Relationship between numeracy and pain burden in parturients using patient-controlled epidural labor analgesia (PCEA): a prospective cohort study

## **Student:** Michael Heffernan, M1, Erik Anderson, M1 **Mentor:** Cynthia Wong, MD; Unyime Ituk, MBBS

Patient health literacy is a critical component of successful patient-physician communication and improved health outcomes. In obstetric anesthesia, efficacy and understanding of patient controlled epidural analgesia (PCEA) may be affected by varying levels of numeracy. With 60% of women choosing epidural analgesia, it becomes imperative that patients understand the treatment process in order to maximize the efficiency and minimize pain. PCEA is the standard of epidural analgesia, and allows pain management to be tailored to the individual. We hypothesized that patients with low numeracy will have worse pain outcomes compared to those with high numeracy. Furthermore, we hypothesized that patients with a low understanding of PCEA will have worse pain outcomes than those with better understanding. Ineffective use of PCEA due to limited understanding may lead to break-through pain and the need for re-dosing of epidural analgesia by an anesthesiologist. Re-dosing is a time consuming activity which can lead to decreased patient satisfaction. Analyzing a potential association with low numeracy and low understanding of PCEA could prompt the standardization of PCEA instruction to patients with low numeracy. Improving understanding may lead to improved pain control and patient satisfaction.

A convenience sample of English speaking, nulliparous women, 18 years or order, were approached after arrival to the labor and delivery unit. Women included in the study were asked to complete the Schwartz 3-item expanded numeracy test and a demographic survey. After the placement of the epidural, pain scores were recorded, using a verbal scale between 1 and 10, every hour until delivery was complete. The day following delivery, subjects were asked to complete a survey evaluating PCEA knowledge, and were asked to rate their overall satisfaction with their labor analgesia. Study subjects were then stratified into two groups, high and low numeracy, based on the results of the Schwartz 3-item test (0-1 correct answer = low numeracy, 2-3 correct answer = high numeracy). The primary outcome was the area under the pain score x time curve (AUC). We assumed a difference of 4.6 in the AUC (baseline  $12.5 \pm 10$ ) represents a clinically significant difference among groups. Assuming that 50% of subjects will have high-and 50% low numeracy, we required 156 subjects to identify this difference.

At this time, a total of 11 subjects have completed the study. 9 subjects were determined to have high numeracy and 2 subjects to have low numeracy. The mean AUC for the high numeracy group was 20.56 and the mean AUC for the low numeracy group was 1.25. Currently, comparison between the two groups cannot successfully be made due to the low enrollment numbers and an unequal distribution among groups. While the current number of enrolled subjects is too low for data analysis, a few trends emerge from the available data. 63.7% of enrolled patients have completed a Bachelor's degree or a higher level of education (2 patients with a doctorate, 3 with a master's, and 2 with a bachelor's), while 18.2% had an associate degree and 18.2% had some college credit but no degree. 100% of the patients enrolled in the study had private insurance. 72.2% were employed for wages, 18.2% were self-employed, and 9.1% were students. Of the patients included in the study, 81.8% were white, 9.1% were Pacific Islander, and 9.1% were South Asian. With continued patient enrollment, further analysis can be made to determine if numeracy impacts pain outcomes in laboring women in relation to their PCEA understanding and use.

#### Antegrade versus Retrograde IV Cannulas for the Aspiration of Blood

Alyssa Heinzman, M2. Mentor: Andrew Feider, MD. Collaborators: Satoshi Hanada, MD; Joshua Godding, M4

#### Background

Drawing blood samples is an important facet of clinical care of patients, both in the inpatient hospital setting and in the operating room. An antegrade intravenous (IV) cannula can aspirate blood, often with a proximal tourniquet to increase venous pressure at the catheter site. However, antegrade IV cannulas have high blood draw failure rates. In the inpatient setting, patients often have blood drawn multiple times per day at a peripheral IV site even though an IV cannula is present for infusion of fluids.

There is a paucity of data on the use of retrograde IV cannulas for aspirating blood. After an extensive PubMed search, only three studies were found regarding relevant information on retrograde cannulation.

Gauger et al. (1984) measured retrograde IV catheters for drug infusions, but did not measure success rates of phlebotomy. Only two studies have directly compared antegrade and retrograde IV cannulas. Rowe et al. (1994) compared retrograde and antegrade IV cannulas for efficacy of insulin sensitivity in blood drawn. Although success rates of blood draws in this study were measured, sample size was extremely small with only 30 subjects receiving retrograde IV cannulas. Mahmoud et al. (2017) compared the incidence of thrombus formation at the tip of antegrade and retrograde IV cannulas, but did not compare the efficacy of drawing blood samples.

Although retrograde IVs could have clinical significance, especially in the inpatient setting, the current lack of research produces difficulty in justifying their use in clinical practice.

#### Hypothesis/Aims

The hypothesis is that compared with traditional antegrade IV cannulas, retrograde IV cannulas will be more successful in drawing 20cc of blood in a two-minute time period, three hours after initial insertion.

The primary outcome of this study is to compare success rates of antegrade and retrograde IV cannulas in their ability to aspirate 20cc of blood in a two-minute time period, three hours after initial insertion. Secondary outcomes include: success rates of aspiration of 20cc of blood at the conclusion of the surgery; success rates of aspiration with tourniquet use; and complication rates (e.g. insertion failure rate, hematoma, erythema, infection, rash, and pain at insertion site).

#### Methods

The study is a double-blinded, prospective interventional study. A sample size of 218 will be used; this will provide an alpha of 0.05 and 90% power. Inclusion criteria are as follows: patients over the age of 18 with a scheduled surgery for over 3 hours duration. Exclusion criteria include: emergency surgery, lateral positioning during surgery, sentinel node dissection or arteriovenous fistula of arm with study IV, and tucking or blood pressure cuff on study IV arm.

The patient is placed under general anesthesia for their operation. The patient is then randomized into the antegrade or retrograde IV cannula group. An anesthesiologist places the peripheral IV cannula and attaches a 33" extension tube with a stopcock. The study IV cannula is then covered with gauze for blinding purposes.

Three hours after the IV cannula has been placed, and again at the conclusion of surgery, a medical student or resident attempts to aspirate 20cc of blood from the stopcock over a two-minute time period. If the aspiration is unsuccessful, a tourniquet is placed proximal to the IV and another aspiration attempt is made.

An anesthesiologist removes the study IV cannula in the post-anesthesia care unit. The patients are contacted on post-operation day one and day fourteen to assess for hematoma, erythema, infection, rash, and pain.

#### Results

At this time, around 50 patients have participated in this study. A data analysis has not yet been completed.

#### **Conclusion/Significance of Research**

This study is filling a significant gap in research and bringing much clinical relevance. Patients, especially in the inpatient unit, often get stuck for blood draws multiple times per day. If retrograde IV cannulas prove to be more successful at aspirating blood, patients could receive one retrograde IV cannula for blood aspiration and need fewer needle sticks during their hospital stay.

## White Matter Microstructure and Behavioral Inhibition in Adolescents: Effects of Family History of Alcohol Use Disorder

Zoe Hildreth, Jatin Vaidya, PhD<sup>1</sup>, Vincent Magnotta<sup>2</sup>, Daniel O'Leary<sup>1</sup> – University of Iowa <sup>1</sup>Department of Psychiatry, <sup>2</sup>Department of Radiology

**Background:** Adolescents with a family history of alcohol use disorder (AUD) score higher on measures of impulsivity and often show deficits in behavioral control. Maturation of brain white matter (WM) is critical for a number of cognitive functions and alterations in WM may contribute to behavioral problems in family history positive (FH+) adolescents (Acheson et al. 2014). WM integrity can be quantified using fractional anisotropy (FA) – a measure of the diffusion of water molecules along a tract in varying directions. Specific WM tracts have been implicated in control including the superior longitudinal fasciculus, splenium of the corpus callosum, uncinate fasciculus, and corticospinal tract. Here, we examine WM microstructure and behavioral impulsivity in FH+ and family history negative (FH-) adolescents.

**Aims:** We sought to investigate differences between FH+ and FH- adolescents on brain WM and impulsivity (measured using a Go/No-go behavioral task).

**Methods:** Data were collected for two adolescent groups aged 13-18: 95 FH+ (47 male, 48 female) and 96 FH- (48 male, 48 female). Inclusion measures required right-handedness, IQ greater than 80, and at least one biological parent diagnosed with AUD for FH+ individuals. FH-adolescents were excluded for diagnosed externalizing disorders (ED) based on self-reporting. All individuals were excluded for use of illegal substances, including alcohol, marijuana, and tobacco if use was above the set screening limit. MRI Diffusion Tensor Imaging data was collected for all individuals and GTRACT was used to estimate FA for tracts of interest. Behavioral impulsivity was assessed using a Go/No-go task. Participants were instructed to press a button when a letter appeared on the screen, but to refrain from pressing the button when the letter "X" appeared. Accuracy data was collected and analyzed for No-go stimulus (letter "X").

**Results:** FH- adolescents showed a trend towards better inhibition on No-go trials. Of the four white matter tracts analyzed, FA was significant between FH- and FH+ groups for only the right and left corticospinal tracts. Median FA data for the right corticospinal tract suggested that FH-subjects had lower FA values (mean=0.389) than FH+ subjects (mean=0.422) when controlling for age and gender (p=0.005). The same trend was observed using median FA data for the L corticospinal tract comparing FH- (mean=0.389) and FH+ subjects (mean=0.416) after controlling for age and gender (p=0.029). Neither FH- or FH+ individuals showed significant correlations between No-go accuracy and FA after controlling for age and gender.

**Conclusions:** The corticospinal tracts of adolescent subjects may be a significant white matter tract impacted by family history of AUD. FH- subjects were shown to have a less cohesive corticospinal tract than FH+ individuals on both the right and left sides. It is unclear how these changes in FA correlate with behavioral inhibition and impulsivity. It is possible that FH+ individuals may exhibit compensatory WM microstructure integrity due to exposure to more impulsive behavior over time. More investigation is needed to explain the cause of varying FA between groups and the impact these white matter tracts have on impulsive behavior.

#### Inflammatory Biomarkers and Cognitive Performance in Smokers: A Pilot Study

Chloe Hlas BA<sup>1</sup>, Gary L. Pierce PhD<sup>2</sup>, Alejandro P. Comellas<sup>1,3</sup>, Rachel Luehrs MS<sup>2</sup>, John D. Newell Jr MD<sup>4</sup>., Eric A. Hoffman PhD<sup>1,4</sup>, Kelsey Warner BA<sup>5</sup>, Anna Croghan MA<sup>5,6</sup>, Peg Nopoulos MD1,<sup>6,7</sup>, Vince Magnotta PhD<sup>1,4,6,7</sup>, Karin F. Hoth PhD<sup>1,6,7</sup>

<sup>1</sup>Carver College of Medicine, U of Iowa; <sup>2</sup>Health and Human Physiology, U of Iowa; <sup>3</sup>Internal Medicine, U of Iowa; <sup>4</sup>Radiology, U of Iowa; <sup>5</sup>Psychology, U of North Dakota; <sup>6</sup>Psychiatry, U of Iowa; <sup>7</sup>Iowa Neuroscience Institute, U of Iowa

**Introduction/Rationale:** Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity, mortality, and disability in the US, with smoking as the most common risk factor. COPD is characterized by airflow limitation that is not fully reversible; however, COPD is a multiple system illness driven, in part, by a chronic enhanced inflammatory process that is believed to begin in the lungs and have systemic effects. Approximately 35-60% of patients with COPD experience cognitive impairment. Although inflammation is known to be elevated in COPD and inflammation is associated with cognitive impairment in other populations, the association between inflammation and cognitive impairment has not been well examined in COPD. In this study, we hypothesized that higher levels of fibrinogen and IL-6 and lower levels of sRAGE among patients with and without COPD would be associated with worse performance on cognitive measures of executive functioning and processing speed, after adjusting for the effects of age, smoking history (pack-years), and severity of airflow limitation (FEV<sub>1</sub> post bronchodilator percent predicted [FEV1pp]).

**Methods:** Nine adults without COPD and 10 adults with GOLD stage 1-3 COPD (without known neurological or cognitive disorders) were recruited from pulmonary research cohorts at the University of Iowa. Participants completed medical history questionnaires, pre- and post- bronchodilator spirometry, a venous blood draw, and comprehensive neuropsychological testing. Fibrinogen, IL-6 and sRAGE were measured in the venous blood using ELISA. Neuropsychological measures were grouped into 5 domains (executive function, processing speed, memory, language, and visuospatial function) and calculated as the mean age-corrected t-score for the tests in each domain (mean of 50 and SD of 10). Associations between inflammatory biomarkers (fibrinogen, IL-6, and sRAGE) and cognitive domain scores were examined using partial correlations adjusting for age, pack-years, and FEV1pp. Basic statistics and partial correlations were performed using SPSS.

**Results:** There were no statistically significant differences in mean age, percentage of females, education, or levels of fibrinogen, IL-6, or sRAGE (all p>0.05) between groups. The COPD group had a significantly greater pack-year history (mean= 6.4 vs 45.9, t=4.9 p < 0.001). The average mean cognitive domain scores for both groups fell within normal limits; however, the COPD group performed approximately 1 SD below those without COPD on cognitive processing speed (mean age-adjusted T-score=50.4 vs 40.2, t=2.9, p=0.009). There were statistically significant associations between IL-6 and executive function (Spearman's rho = -0.52, p = 0.037; rho was calculated as IL-6 was not normally distributed); fibrinogen and both language (r = -0.64, p = 0.008) and processing speed (r = -0.56, p = 0.026); and sRAGE and memory recall (r = -0.54, p = 0.033) after adjusting for age, pack-years and FEV1pp.

**Conclusions:** We observed associations between inflammatory markers (IL-6, fibrinogen and sRAGE) and cognition after adjusting for age, smoking history, and FEV<sub>1</sub>pp in our sample that provided modest support for a link between inflammation and cognition in smokers. Several associations were consistent with expectation; however, the correlation between sRAGE and memory recall was in the opposite direction of our prediction. The past literature is mixed regarding expected levels of sRAGE in COPD with some research suggesting that higher levels of sRAGE are linked to elevated cardiovascular disease risk. Current study results were likely affected by limitations from the small sample size and some smoking history among participants without COPD. This pilot study underscores the importance of further research exploring mechanisms beyond primary pulmonary physiology, such as inflammation, in relation to cognition, but larger samples with a broader range of illness severity are needed to draw firm conclusions about the association.

## Instituting a Restrictive Opioid Prescribing Protocol for Primary Total Hip and Knee Arthroplasty: One Institution's Experience

Andrew J. Holte, Christopher N. Carender, Nicolas O. Noiseux, Jesse E. Otero, Timothy S. Brown

**Introduction:** Orthopedic surgeons overprescribe opioids postoperatively. In 2018, our practice began following AAOS guidelines for prescribing opioids following primary total hip and knee arthroplasty (TJA). We sought to: 1) describe historical prescribing patterns after TJA; 2) describe our experiences instituting a restrictive opioid prescribing protocol; 3) compare results and clinical outcomes before and after protocol implementation.

**Methods:** We retrospectively reviewed primary TJA from 2017 to 2018. Two cohorts were created: a historical cohort (surgery prior to prescribing protocol implementation; 282 patients) and a restrictive cohort (surgery after prescribing protocol implementation; 117 patients). All patients received periarticular or regional block at the time of surgery, and opioid use in the perioperative and postoperative periods was recorded in morphine milligram equivalents (MMEs). Outcomes were assessed with KOOS Jr, HOOS Jr, and PROMIS scores.

**Results:** The two cohorts were not significantly different in any preoperative measure, including prior opioid exposure (p=0.64). Perioperative opioid use (85% vs 80%, p=0.28) and postoperative inpatient opioid use ( $4.7\pm3.0$  MME/hr vs.  $4.5\pm2.9$  MME/hr; p=0.47) were not significantly different between cohorts.

Patients in the historical cohort were given significantly larger initial prescriptions than patients in the restrictive cohort (751.5 $\pm$ 296.6 MMEs vs. 387.3 $\pm$ 202.2 MMEs; p<0.01). Patients in the historical cohort received significantly more refills per patient (0.5 $\pm$ 0.8 refills vs. 0.3 $\pm$ 0.5 refills, p=0.02), and a greater overall quantity of medication through refills (253.0 $\pm$ 447 MMEs vs 84.0 $\pm$ 166 MMEs, p<0.01). The number of phone calls per patient regarding pain or pain medication was significantly less in the restrictive cohort (0.7 $\pm$ 1.4 calls/patient vs. 0.4 $\pm$ 0.7 calls/patient, p=0.02). Clinical outcome measures were not significantly different between cohorts.

**Conclusions:** Drastic reductions in opioid prescriptions following TJA are possible without an increase in refills, phone calls, or adverse clinical effects. Patient education regarding opioid medication and expectations set preoperatively are important for successful implementation.

## Alcohol Consumption's Effects on Heart Rate Variability in Endurance Athletes during a One Week Endurance Cycling Event

Conor Houlihan, M2 Britt Marcussen, MD (mentor)

**Introduction**: Heart rate is the average number of heart contractions per minute. Heart rate variability (HRV) measures how much variation in time there is between those beats. HRV is considered a reliable and non-invasive tool to measure physiologic stress [1]. The body responds to physiologic stress through the balance between the opposing branches of the autonomic nervous system, the sympathetic and parasympathetic systems. Stress will increase the activity of the sympathetic system, having many effects on the body including decreasing HRV. Activation of the parasympathetic system has the opposite effect of increasing HRV. For example, physiologic stress such as smoking, history of heart attack, and chronic illness have been shown to decrease HRV [2-4]. Conversely, middle-aged individuals who have maintained good cardiovascular health have greater HRV [5].

Alcohol consumption has been demonstrated to increase HRV by modulating the interaction of the two branches of the autonomic nervous system. [6,7] In a similar manner, aerobic exercise has been demonstrated to increase HRV by augmenting parasympathetic modulation [8,9]. There have been no studies investigating the effects of concurrent high-endurance exercise and alcohol consumption on HRV. The Register's Annual Great Bicycle Ride Across Iowa (RAGBRAI) provides a unique opportunity to study alcohol's effects on endurance athletes due to the self-selecting nature of the 468 mile bike race and its reputation for regular alcohol consumption during the seven day event. [10]

**Hypothesis**: There is a statistically significant interaction between an endurance athlete's HRV and alcohol consumption while they are participating in a week long endurance cycling event.

**Methods**: Inclusion criteria included that subjects ride all seven days of RAGBRAI. Exclusion criteria included subjects with a diagnosed heart condition and subjects taking a medication that altered cardiovascular function. An alcohol consuming exposure group and a non-alcohol consuming control group were followed from their enrollment in the study to the conclusion of RAGBRAI with team members taking each subjects HRV every morning followed asking the subject to report their alcohol consumption in standard alcohol drinks (12oz beer, 5oz wine, 1.5 oz hard liquor). The intention was to enroll equal numbers of control and exposure subjects.

A linear mixed effects model was fit to the data with random effects for subjects to account for underlying individual heart health or drinking habits. A random slope was fit to allow for differing HRV values between subjects outside of drinking while a random slope was included to allow for drinking to have different effects on different subject's HRV measures. It should also be noted that the number of drinks consumed was used as the predictor variable to use the most information as possible and avoid labeling a group "control" when they were exposed to alcohol. Instead, drinkers were dichotomized into "light" and "heavy" groups for illustrative purposes in tables and plots. Due to non-compliant alcohol consumption in the control group, the control and exposure groups are referred to as "light drinker group" and "heavy drinker group" to better reflect each group's alcohol consumption status.

**Results**: Between 62% and 100% of subjects had values for recorded in a given day. Due to non-compliance alcohol consumption in the control group Average drinks consumed for the light group ranged from 0 to 1.4 drinks per day, while average drinks consumed for the heavy group ranged from 3.5 to 18.13 drinks per day. Average HRV was consistently higher in the light drinking group, ranging from 58 to 78.8, while HRV in the heavier drinkers ranged from 48.9 to 66.22. Both drinks consumed and HRV increased over the course of the study for the majority of the subjects. The average random effects were not significantly different between the light and heavy drinkers.

**Conclusions:** No statistically significant interaction between alcohol consumption and HRV in the context of a multiple day endurance event such as RAGBRAI was found, but biases, missed record points, and confounding variables are a major issue of this study.

**Title:** Effects of region-specific knockouts of *Ndufs4* on volatile anesthetic response **Authors:** Jessica Hui, Renjini Ramadasan-Nair, Pavel Zimin, Leslie Itsara, Philip Morgan, Margaret Sedensky

Principal Investigators: Philip Morgan, Margaret Sedensky

Background: Anesthesia is a complex phenomenon characterized by amnesia, analgesia, immobility and loss of consciousness. Anesthetic mechanisms are not well understood at several levels of neuronal function. These include the molecular binding targets, the disrupted physiological mechanisms, the brain regions involved, and the altered neuronal circuitry systems. Previous reports have shown that defects in mitochondrial complex I profoundly hypersensitize C. elegans, mice and children to volatile anesthetics. In addition, complex I function is uniquely sensitive to volatile anesthetics in concentrations that correlate with the whole animal EC50s of the respective species. Mice featuring a global knock out of the mitochondrial protein NDUFS4 display biochemically proven complex I specific mitochondrial dysfunction. This animal, Ndufs4(KO), displays the greatest volatile anesthetic hypersensitivity yet reported for any mammal. The sensitivity is recapitulated by glutamate-cell specific KO of the gene in the CNS. It is well documented that anesthetics lower the cerebral metabolic rate in an agent- and region-specific manner. However, whether this is a cause or effect of the anesthetized state is controversial. Changes in anesthetic sensitivity seen in Ndufs4(KO) mice favor the model that a lowered metabolic rate causes the anesthetic state. However, it remains possible that compensatory developmental changes in the constitutive global Ndufs4(KO) may also play a role in determining anesthetic sensitivity.

**Purpose/Aims**: To determine whether the inhibited metabolic state of specific regions of the CNS causes the anesthetic phenotype, and to eliminate early developmental changes resulting from the global loss of *Ndufs4*, we postnatally knocked down *Ndufs4* in specific CNS regions in mice with normal volatile anesthetic sensitivity.

**Methods:** In mice carrying an *Ndufs4lox*/lox gene, adeno-associated virus expressing Cre recombinase was stereotactically injected into regions of the brain postulated to affect sensitivity to volatile anesthetics (central/dorsal medial thalamus, vestibular nucleus, parietal association cortex, mesopontine tegmental anesthetic area). These injections generated otherwise phenotypically wild type mice with region-specific, postnatal inactivation of *Ndufs4*, minimizing developmental effects of gene loss. Sensitivities to the volatile anesthetics isoflurane and halothane were measured using loss of righting reflex (LORR) and movement in response to tail clamp (TC) as endpoints.

**Results:** Knockdown of *Ndufs4* in the vestibular nucleus produced resistance to both anesthetics for movement in response to TC. *Ndufs4* loss in the central and dorsal medial thalami and in the parietal association cortex increased anesthetic sensitivity in both TC and LORR. Knockdown of *Ndufs4* only in the parietal association cortex produced striking hypersensitivity for both endpoints, and accounted for half the total change seen in the global *Ndufs4* knockout. Excitatory synaptic transmission in the parietal association cortex in slices from *Ndufs4*(KO) animals was hypersensitive to isoflurane compared to control slices.

**Conclusion:** We identified a direct neural circuit between the parietal association cortex and the central thalamus, consistent with a model in which isoflurane sensitivity is mediated by a thalamic signal relayed through excitatory synapses to the parietal association cortex. We postulate that the thalamocortical circuit is crucial for maintenance of consciousness and is disrupted by the inhibitory effects of isoflurane/halothane on mitochondria.

## Abstract

## Differences in characteristics and outcomes between married and unmarried patients undergoing radical cystectomy for bladder cancer

Chermaine Hung BS<sup>1</sup>, Conrad Tobert MD<sup>1</sup>, Nathan Brooks MD<sup>1</sup>, Lewis Thomas MD<sup>1</sup>, Sarah Mott MS<sup>2</sup>, Michael Brumm BS<sup>2</sup>, Kenneth G. Nepple MD FACS<sup>1,2</sup>

<sup>1</sup>Department of Urology, University of Iowa Health Care, Iowa City, Iowa <sup>2</sup>Holden Comprehensive Cancer Center, Iowa City, Iowa

**Objectives:** Radical cystectomy (RC) for bladder cancer is associated with a significant risk of complications and mortality. Understanding the factors that contribute to cystectomy outcomes improves risk assessment for patient counseling and may provide insight into future care interventions. Being married has been reported to be a protective factor in cancer, but most reports are from cancer registry data which lacks information on factors such as medical comorbidity. Using an institutional cohort, we sought to expand on prior work to further evaluate the differences in patient disease-specific characteristics between married and unmarried cystectomy patients, and to report the association of marital status with postoperative complications and mortality.

**Methods and Materials:** 334 patients underwent radical cystectomy at our institution between 2000 and 2010. Marital status was identified prospectively by cancer registrars at the time of treatment. Marital status was defined as married versus unmarried (single, widowed, or divorced). Variables assessed were patient demographics, driving distance to our institution, comorbidity (defined by Charlson Comorbidity index), body mass index, tumor staging, and treatment (neoadjuvant chemotherapy and type of urinary diversion). Outcomes measured were length of stay, discharge status (to home or to a facility), 30-day postoperative complications, and 4-year mortality. Statistical analysis was performed using univariate analysis, and multivariate analysis was used to adjust for measured differences. Kaplan-Meier analysis was conducted to predict 4-year overall survival.

**Results:** On univariate analysis, unmarried patients were more likely to be female (p<0.01), to have increased comorbidities (p<0.01), and to have undergone an ileal conduit urinary diversion (p=0.048). Age, body mass index, clinical disease stage, and rate of neoadjuvant chemotherapy were not significantly different between married and unmarried patients (p>0.05). Unmarried patients were more commonly node positive (p=0.06), but this difference was not statistically significant. With respect to outcomes, the rate of postoperative complications was not higher in unmarried patients (p=0.05); however, being unmarried was associated with a longer length of stay (p=0.029) and with discharge to a facility (p<0.001). The 4-year mortality was higher in unmarried patients (p<0.001) with the most pronounced difference in the first 3 months after surgery. On multivariate analysis, being unmarried was a predictor of increased mortality (p=0.047). Being unmarried was associated with increased odds of longer length of stay (p=0.002) even after adjusting for differences in age, gender, comorbidity, and diversion type.

**Conclusions:** In patients undergoing radical cystectomy for bladder cancer, unmarried patients differed in baseline characteristics and treatment choices from married patients. Even after adjusting for differences in baseline characteristics and treatment choices, unmarried patients had worse outcomes, including longer length of stay despite equal complication rate, increased discharge to facility, and increased mortality.

## Project Title - Characterization of Non-Syndromic Hearing Loss in a Family with Suspected vGLUT3 Mutation

M2 Student: Heba Isaac Research Mentor: Marlan Hansen, MD and Andrew Liu, MD The University of Iowa, Department of Otolaryngology

### Abstract

Normal hearing requires the functional compliance of all parts of the auditory system. Interruptions in any part of the system can result in hearing impairments (HI). Many factors can contribute to HI with the primary causes attributed to aging, noise exposure, or genetic factors, and these factors often interact. The auditory vestibular system utilizes glutamatergic neurotransmitters that are packaged in vesicles and transported via glutamate transporter 3 (vGLUT3) to presynaptic active zone and exocytosed using specialized ribbon synapses. Therefore, vGLUT3 expression has an essential role in the function of the auditory pathway. Mutations in *SLC17A8*, the gene encoding vGLUT3, thus, can result in HI with varying severity depending on the type of genetic modification. Mutations in *SLC17A8* have been linked with DFNA25, an autosomal dominant non-syndromic hearing loss (ADNSHL) in humans. Such patients are expected to have an auditory neuropathy (AN) phenotype. Patients with AN have highly variable (and often poor) outcomes with cochlear implantation. The character of HI (age of onset, rate of progression, frequencies involved, speech understanding, etc) for patients with *SLC17A8* mutations remains poorly characterized. In addition to standard hearing rehabilitation options such as hearing aids or cochlear implants, there is lively interest in gene therapy for hearing loss because it offers the possibility to restore the expression of the defective genes. Recent studies have demonstrated that mice lacking vGLUT3 via targeted deletion of *SLC17A8* gene lacked auditory nerve responses to acoustic stimuli, although otoacoustic emissions (OAE) were present, similar to human AN phenotype.

At the University of Iowa we have the largest genetic database of patients undergoing cochlear implantation in the world. One family in the database has an identified mutation in *SLC17A8*. The present study attempted to understand the nature and progression of the hearing loss in this family with a known *SLC17A8* mutation and inform the potential use of gene therapy as a therapeutic alternative to conventional prosthesis.

### Aims

SA1 - Characterize the timing and nature of hearing loss in a family with SLC17A8 mutation.

SA2 – Determine the effectiveness of different hearing rehabilitation options to restore auditory perception.

#### Methods

Family data – The family in the study was ascertained through the University of Iowa Department of Otolaryngology. To characterize the pattern of hearing loss, detailed family history will be obtained through pedigrees, questionnaire, and personal interviews. Multigeneration audiograms will also be reviewed for most family members.

Genotyping and linkage analysis – Saliva samples will be collected, and multipoint linkage analysis will be performed.

The effectiveness of various rehabilitation options (HAs, CI, hybrid CI) will be evaluated via personal interviews with family members to assess speech understanding and social interactions. Different rehabilitation options include hearing aids, cochlear implant, and hybrid cochlear implant.

### **Results & Discussion**

Due to delays with the Institutional Board Review application, the project was on hold until it was approved just recently. However, throughout the summer, I worked with Dr. Andrew Liu on a separate project looking at whether there are risk factors that predispose individuals to lose their residSuspected ual hearing after cochlear implant surgery. The project is still ongoing and preliminary data will be presented during Medical Student Research Day.

## Akansha Jain Mentor: Dr. Michael Henry Title: Utilizing ferroptosis to target therapy-resistant cancer cells

The epithelial to mesenchymal transition (EMT) is a normal physiological process by which cells of epithelial origin convert into cells bearing mesenchymal characteristics. It is hypothesized that EMT phenotypes are associated with aggressive and advanced disease, cellular invasion, metastasis, and resistance to commonly used chemotherapy drugs. Cancer metastasis remains the major driver of mortality in patients and therefore targeting an EMT phenotype may be a new approach to treat metastatic disease. Glutathione peroxidase 4 (GPX4) inhibitors were recently identified as a class of compounds that selectively target therapy resistant cancer cells exhibiting a mesenchymal phenotype. GPX4 catalyzes the reduction of toxic lipids peroxides to their corresponding non-toxic alcohols which eventually causes the dissipation of reactive oxygen species within the cell and protects cells against ferroptotic death. Inhibiting this pathway by inhibiting GPX4's enzymatic activity can therefore induce ferroptosis. Through this study, we identify metabolic differences in cells exhibiting the EMT phenotype, TEM 4-18 cells, compared to cells exhibiting an epithelial phenotype, PC-3E cells. First we show that TEM 4-18 cells are more sensitive to the GPX4 inhibitors RSL3. ML162, and ML210. This sensitivity is reversed when the cells are coincubated with inhibitors to the ferroptosis ferrostatin-1 and liproxstatin-1. In addition, knocking-out ZEB1, a transcription factor associated with the mesenchymal phenotype also reverses this increased sensitivity to GPX4 inhibitors. We show that there are significantly lower amounts of reduced glutathione (GSH), a co-factor of GPX4, in the TEM 4-18 cells. Lastly, through RT-gPCR we show that the gene expression of cystathionine-beta-synthase (CBS), an enzyme that is required for intracellular synthesis of a precursor of glutathione, is upregulated in TEM 4-18 cells. Knocking-out ZEB1 reverses both of these phenotypes. These metabolic differences may provide a mechanistic explanation to why EMT cells exhibit an increased sensitivity to GPX4 inhibitors.

#### Role of PAK Signaling in Vemurafenib Resistant Melanoma

M1 Student: Brooke Jennings Research Mentor: Christopher Stipp, PhD

**BACKGROUND:** Mutations in the B-RAF gene account for approximately 50% of genetic driver mutations in skin melanoma. Patients with B-RAF mutant melanoma are typically treated with a targeted drug called vemurafenib. However, patients can stop responding to this treatment in as little as six months. PAK, also known as p21-activated kinase, is a possible contributor to vemurafenib resistance because of its potential to activate YAP and TAZ, proto-oncogenic transcriptional co-activators that are the targets of the Hippo tumor suppressor pathway. PAK signaling works downstream of the monomeric GTPase Rac1 to promote F-actin accumulation, a known regulator of YAP and TAZ activation. This potential pathway may explain the upregulation of YAP and TAZ and the actin remodeling seen in resistant cells.

**PURPOSE:** Previous research conducted in the Stipp lab has shown that a PAK inhibitor can prevent vemurafenib resistance in the A375 cell line. The <u>objective</u> of this study was to determine the role of specific PAK kinase isoforms in vemurafenib resistant melanoma and establish the generality of PAK-induced resistance using additional BRAF mutant cell lines. Our <u>hypothesis</u> was that one or more PAK isoforms is required for the emergence of vemurafenib resistance. We used a combination of pharmacological, genetic and biochemical approaches to test our working hypothesis.

**METHODS:** A375 and 451 LU are BRAF-mutant melanoma cell lines that can be used to model vemurafenib resistance *in vitro*. In previous experiments in the Stipp lab, FRAX 486 in combination with vemurafenib has prevented the development of drug resistant cells. Lysates were prepared from cells treated for extended periods with FRAX 486. To identify specific PAK kinase isoforms contributing to resistance, levels of each group I isoform (PAK 1, 2, and 3) were measured in the cell lines, and isoforms that were present were depleted using retroviral shRNA vectors. The PAK1-specific G-5555 compound was also utilized to determine whether targeting PAK1 alone would prevent vemurafenib resistance. The effects of drug treatments and PAK knock down in cells were evaluated using the AlamarBlue reagent, which yields relative tumor cell number as a read out. Immunoblotting was conducted to determine levels of relevant signaling proteins, such as phospho-MEK S217 (a readout of BRAF activity), phospho-MEK S298 (PAK kinase readout), and blots were quantified using a LiCOR blot imager.

**RESULTS:** Biochemical lysates of 451 LU cells treated with vemurafenib exhibited a strong upregulation of p-MEK (S298). By Day 25 in long term lysates a significant decrease is seen in the following protein levels: p-MEK (S217/S221), PAK1, PAK2, p-PAK1 (S199/204), p-PAK2 (s192/197), and active  $\beta$ -catenin. PAK1 and PAK2 isoforms were identified in both the A375 and 451 LU cell lines. PAK knock-downs were created for PAK1 and PAK2 using shRNA vectors; however, the PAK knock down cell lines provided inconclusive results in AlamarBlue experiments taken out to day 18. Dose response curves for the G-5555 compound in both the A375 and 451 LU cell lines indicated IC<sub>50</sub> values of approximately 5  $\mu$ M and 8  $\mu$ M, respectively. AlamarBlue experiments with the G-5555 compound in A375 and 451 LU yielded inconclusive results when taken out to day 14. The FRAX 486 compound was also used to create a dose response curve and signal inhibition curve in 451 LU cell line, indicating IC<sub>50</sub> values of 500 nM and 1 $\mu$ M, respectively.

**CONCLUSION:** PAK1 is the dominant isoform in both A375 and 451LU, while PAK2 is also present at low levels. Inhibition of PAK1 alone is a potential therapeutic target. G-5555 would allow for a more specific target than FRAX 486 which targets all group 1 PAK isoforms. It appears the mechanism by which PAK inhibition blocks resistance is occurring at a sub-detectible level in the short term, but builds up over time. This explains the strong depletion in p-MEK (S217/S221), PAK1, PAK2, p-PAK1 (S199/204), p-PAK2 (S192/197), and active  $\beta$ -catenin by day 25 of treatment of vemurafenib and FRAX 486 combination. The AlamarBlue experiments yielded inconclusive results, however these experiments were only taken out to roughly day 14. Based on previous data in the Stipp lab, cell viability differences between vemurafenib and vemurafenib + FRAX treatments were not seen until around day 25. After the results seen in both the biochemical long term assays and previous population doubling experiments it is rational that the AlamarBlue experiments need to be taken out to at least day 25 to see more significant results. The new cell line 451 LU is also ready to be tested with the appropriate FRAX 486 concentration (200 nM - cell viability IC<sub>20</sub>) to confirm utility of treatment across cell lines.

Novel Drug Candidate for Parkinson's Disease Stimulates the Glycolytic Enzyme PGK1

<u>Andrew Kalenkiewicz</u><sup>1,4</sup>, Sarah Ernst<sup>2,3,4</sup>, & Michael Welsh<sup>2,3,4</sup> <sup>1</sup>Medical Scientist Training Program <sup>2</sup>Department of Internal Medicine <sup>3</sup>Howard Hughes Medical Institute <sup>4</sup>Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, IA

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting over 10 million people worldwide. In spite of a pressing need for therapeutic options, there have been very few successes in the field of PD drug discovery. Terazosin, a small molecule drug approved in 2004 for the treatment of benign prostatic hyperplasia (BPH), was recently shown to have therapeutic potential in animal models of PD. The mechanism of Terazosin's therapeutic effect in BPH stems from its inhibition of the  $\alpha$ 1 adrenergic receptor, but its effect in PD models has been traced to a novel mechanism—i.e. stimulation of the glycolytic enzyme phosphoglycerate kinase 1 (PGK1). More specifically, low doses of Terazosin were found to increase ATP generation in neurons and protect against neurodegeneration mediated by apoptosis. Meanwhile, high doses of Terazosin inhibit PGK1 ATPase activity in vitro and in vivo. We developed a novel assay that confirms this biphasic behavior, and furthermore shows that it extends to multiple other drugs in the same structural family as Terazosin. The potency and magnitude of this biphasic activity varies across the small molecule class, a finding that we anticipate will be useful in developing a clinically safe and active drug. Our future work will aim to develop a small molecule that exhibits minimal  $\alpha 1$  antagonism but can still protect against neurodegeneration at low doses. Most notably, Terazosin's  $\alpha 1$  activity predisposes it to adverse side effects like orthostatic hypotension. This is a major potential pitfall for a drug aimed at treating PD patients, who already suffer from motor disability. Our strategy can minimize this effect and expedite the development of a safe therapeutic for PD patients.

**Clinical outcome of pancreatic cancer patients with indeterminate pulmonary nodules** Austin G. Kazarian<sup>1</sup>, Sarah L. Mott<sup>2</sup>, Carlos H.F. Chan<sup>1,2</sup> <sup>1</sup> Department of Surgery, <sup>2</sup> Holden Comprehensive Cancer Center, University of Iowa, Iowa, IA

**Background:** Pancreatic cancer is the fourth leading cause of cancer related death in the United States. While surgery is the only potentially curative treatment, patients often present with advanced stages of disease, making them non-surgical candidates based on pre-operative CT imaging studies. Indeterminate pulmonary nodules (IPNs) are often visualized on these scans and pose a conundrum for the treating medical oncologists and pancreas surgeons since pancreatic resection is generally contraindicated in the metastatic setting. Some studies have suggested that only a small fraction of these nodules develop into true lung metastasis. In this study, we aim to determine the clinical outcome of pancreatic cancer patients with IPNs undergoing curative resection.

<u>Methods</u>: A retrospective analysis of 4690 patients with hepatopancreaticobiliary malignancies in the Holden Comprehensive Cancer Center Oncology Registry between 2007 and 2017 was conducted. From this database, 1182 patients with pancreatic ductal carcinoma were identified and reviewed. Survival probabilities were estimated using the Kaplan-Meier method. Time was calculated from diagnosis to death due to any cause for overall survival (OS), and from operation to recurrence for recurrence-free survival (RFS). Cox regression models were used to assess the effects of demographic, clinicopathologic, and treatment variables on OS and RFS.

**<u>Results:</u>** Of 1182 patients, only 232 patients underwent surgical resection; 50 of them had IPNs preoperatively. Forty-three patients (86%) had pancreatoduodenectomy and 7 (14%) had distal pancreatectomy. Twelve patients (24%) received neoadjuvant therapy and 35 patients (70%) received adjuvant therapy. Negative margins were obtained in 82% of patients. Forty-four patients (88%) had stage II disease and 6 had stage 0/I disease. Over a median follow-up from the time of diagnosis of 20 months, 37 patients (74%) developed local recurrence or distant metastasis in liver (38%), lung (32%), peritoneum (8%), or other site (8%). For the entire cohort, median RFS was 14 months and median OS was 23 months. Tumor size (HR 1.56, CI 1.23-1.98, p < 0.01) and elevated pre-operative CA19-9 levels (HR 2.51, 1.22 – 5.15, p = 0.01) were associated with lower RFS. Tumor size (HR 1.43, CI 1.10-1.86, p < 0.01) and diabetes (HR 2.05, CI 1.02-4.11, p = 0.04) were associated with lower OS. Although not statistically significant, patients with lung only recurrence tended to have superior OS relative to other single sites (HR 2.05, CI 0.66-6.33, p = 0.21) or multiple sites (HR 2.30, 0.75-7.50, p = 0.15) while remaining inferior to no recurrence (HR 0.39, CI 0.09-1.60, p = 0.19). Indeed, patients with lung only recurrence had a median survival after recurrence of 17.9 months compared to 6.5 months for other single sites or 4.3 months for multiple sites.

**Conclusion:** Although our cohort is small, it supports previous studies that suggest only a portion of IPNs develop into true lung metastasis and that isolated lung metastatic recurrence may confer a better survival over metastasis of other sites. Ongoing efforts will compare survival of resected vs. non-resected patients with IPNs and identify serum biomarkers and clinical predictors in the hopes of providing future guidance in clinical practice.

## Evaluation of clinical fall risk screening tools by comparison to center-of-pressure derived postural stability measurements

University of Iowa Carver College of Medicine, Department of Internal Medicine PI: Sawyer Kieffer; Mentor: Philip Polgreen, MD

**Background:** Falls among hospitalized patients can lead to longer hospital stays, loss of functional status, and excess hospital costs. Common screening tools for fall risk (e.g. the Morse Fall Scale, the Hendrich Fall Risk Model II and STRATIFY) use a scoring system to capture many variables associated with fall risk. However, traditional screening tools lack an adequate balance of sensitivity and specificity to reliably assess fall risk. Thus, there is a need for new clinical tools for fall-risk identification. Center-of-pressure variations function as measures of static posturography and have been associated with fall risk, and prior investigators have demonstrated that the Wii Balance Board (WiiBB) is a reasonable alternative to expensive force-plate systems.

**Methods:** Participants recruited from University of Iowa Hospitals and Clinics general medicine service were evaluated using four fall risk assessment tools: STRATIFY, Morse Fall scale, Iowa Fall Risk index, and an Australian fall risk tool. Participants also completed the Modified Vulnerable Elders Survey and a grip-strength test. The WiiBB is a rectangular platform, which is slightly larger than a bathroom scale and incorporates 4 separate force sensors under the top plate. We have designed and implemented custom software (written in Python v3.5) that collects data via Bluetooth from the WiiBB's force sensors. Participants are specifically asked to complete the series of 4 tests on a WiiBB for 30 seconds each: (1) eyes open, feet apart; (2) eyes open, feet together; (3) eyes closed, feet apart; and (4) eyes closed, feet together. The software chooses the order of the tasks for each subject and allows 30 seconds of rest between each test. 11 WiiBB features were evaluated: range of x, range of y, standard deviation (sd) of x, sd of y, mean displacement vector length, sd of displacement vector length, mean speed, sd of speed.

**Results:** 32 participants (17 male/15 female, ages 56-94) completed the protocol. There was essentially no variability in the standardized fall-score instruments. The balance-board data are weakly-to-not-correlated with the fall-instrument scores. 11 features were considered by each condition/instrument combination. Among these different features of balance, we observed variation between different patients.

**Discussion:** Due to the lack of variability in standardized fall-prediction instruments we were unable to compare our WiiBB features against standard measurements of fall risk. This finding highlights an important shortcoming in current methods of fall-risk assessments: current fall-risk-assessment tools frequently do not appear to capture variability in fall-risk factors. Given the ability of the WiiBB to measure subtle variations in postural stability, future work should investigate how these variations can be used to predict fall risk among hospitalized patients.

# Determinants of Health-Care Utilization for Symptomatic RTIs in Rural Indian Women

## Mitch Kinkor, BSBA, Kelly Baker, PhD

**Introduction:** Reproductive tract infections (RTIs) cause a great public health burden worldwide, and that burden is amplified because health-care seeking for treatment of RTIs is currently inadequate for resolution of disease. Many socioeconomic factors impact a woman's likelihood to seek treatment, but there are gaps in knowledge about whether these factors stem from general challenges with health care access versus women's response to gender-specific disease symptoms. This project aims to identify determinants of care seeking behavior and analyze the difference of utilization of health care resources in response to RTI symptoms and general symptoms to provide more information on potential target populations for interventions that promote care seeking behavior.

**Methods:** Our analysis uses data from a cross-sectional, population-based surveillance survey investigating demographics, personal hygiene health habits, gynecological health, and health care seeking behavior in response to symptoms was conducted with rural, non-pregnant women in Odisha, India, from 2013-2014 (n = 3,600). We utilized logistic regression techniques to determine important variables that impact a woman's likelihood to seek treatment. Variable selection was aided by the construction of a directed acyclic graph.

**Results:** Of the 342 respondents that self-reported RTI symptoms, 161 women (47.1%) reported that they sought care for those symptoms, compared to 204 women (59.6%) who reported to have sought medical care the last time they had symptoms of an adverse non-reproductive disease. Full model analysis showed that previous health-care seeking behavior in response to general symptoms, status as a married woman, and living in a household with more than one sleeping room were shown to be significant predictors of health-care seeking behavior for RTI symptoms. There was no association between education level or possession of a Below Poverty Line (BPL) Card and health care seeking behavior. When those who did not seek treatment for RTI symptoms were asked why they did not seek treatment, the overwhelming majority (73.8%) reported they did not think they needed treatment for their symptoms, followed by inability to take time off from work (8.5%).

**Discussion:** Interventions aimed at increasing health-care seeking behavior in Indian women should be targeted at unmarried women who are less likely to use formal providers for general health care, and those interventions should focus on reproductive health education.

## Identification and Analysis of Leishmania exosome-associated proteins and patient demographic information in Natal, Brazil

Michael R. Klemme, Joyce Wahba, Selma M.B. Jeronimo and Mary E. Wilson University of Iowa Carver College of Medicine 2018.

## Introduction

Visceral Leishmaniasis (VL), a parasitic disease caused by the protozoan *Leishmania infantum*, is emerging in a periurban pattern throughout Brazil, including the northeastern city of Natal. The prevalence of symptoms ranges from 1-25% depending on the geographical region, population, and *Leishmania* species. Known risk factors include poverty, contact with an infected person, dogs in the house/immediate neighborhood, and immunocompromise. Males are more likely to acquire disease than females, although the rate of infection (assessed by skin test or serology) is nearly equal. Regardless of positive or negative symptoms and independent of successful treatment, an individual may harbor the parasite for life. *Leishmania* spp. protozoa are harbored by dog reservoirs and transmitted by sand fly vectors to human hosts, where they can infect and influence a range of host immune cells during and after acute infection. Leishmania parasites releases exosomes, a type of uniformly sized small vesicle of 40-100 nm that contains protein, miRNA, and lipids. Exosomes are found in all body fluids and are becoming recognized as a major means by which cells transfer their content and communicate with other host cells, providing a mechanism by which pathogens may systemically affect their host.

## **Purpose of the Study**

We hypothesized that Leishmania parasites exosomal protein content incorporates into the exosomes released from host cells found within the circulation of patients with acute VL. The study of exosomes and their contents, therefore, would provide targets for novel diagnostic antigen tests. Our aims of this project were as follows: (1) Isolate exosomes from *L. infantum*-infected symptomatic (VL+) and asymptomatic (AL) patients in Natal, Brazil, as well as collect exosomes from endemic negative uninfected controls (C). (2) Investigate whether blood-derived exosomes contain parasite proteins recognized by serum from patients with VL. (3) Extract exosomes to be brought to the University of Iowa for analysis of protein and RNA content. (4) Determine the demographic characteristics of subjects used for exosome isolation.

### Methods

<u>Serum samples</u> from human and dog VL+, human AL, and healthy negative Brazilian human and dog controls were used. <u>Demographic characteristics</u> were extracted from laboratory records. Human subjects were identified by sample number and obtained from paper records supplied by the Jeronimo lab. Subjects were categorized into 3 groups: (1) patients with VL+ acute infection with positive symptoms and serology, (2) subjects with AL infection detected through positive serology but no VL symptoms, (3) Control uninfected Brazilians. Study subjects are entered into protocols approved by the NIH, the local IRB and the University of Iowa. <u>Exosome isolation</u>: The Solution Biosciences Exoquick Exosome Precipitation isolation was used as described by the manufacturer. Briefly, exosomes were isolated by centrifugation, addition of precipitation solution to supernatants, incubation at 4°C, and centrifugation of the pellet. Exosomes were suspended in PBS and stored at -20°C (short term) or -80°D (long term storage). Exosome protein concentration was analyzed by Nanodrop using the Sigma-Aldrich Bicinchoninic Acid protein assay kit (BCA). <u>Data analysis was conducted using Graph Pad Prism 7</u>.

#### Results

The mean $\pm$ SD of exosome protein concentrations are as follows: Human VL+ were 39.5 $\pm$ 19.29 (n=80); AL 23.55 $\pm$ 11.68 (n=34); C 19.09 $\pm$ 15.27 (n=28); Dog VL+ 72.03 $\pm$ 25.85 (n=35); C 45.31 $\pm$ 19.98 (n=35). Of VL+ patients, 42.8% of pre-pubertal (age 0-11) patients, 37.21% of patients aged 12-49, and 30.77% of patients 50+ were male. In AL subjects, 0%, 44.19% and 23.08% of individuals aged, 0-11, 12-49 and 50+, respectively, were male (n=70).

#### Conclusion

VL+ dogs have the highest circulating exosome protein concentration, with a trend towards infected patients having a higher protein concentration than controls. Overall, males dominated our subset of Age vs Sex data, reinforcing previous studies showing a male dominant infection pattern of VL. Although incomplete, our demographic results were consistent with published studies. The most common symptoms of leishmaniasis observed were fever, weight loss, fatigue, and hepatosplenomegaly, while the major risk factors were having dogs in the home or neighborhood and having contact with a VL+ patient. Many AL subjects also frequently donate blood and although not yet recognized, could present a new risk of spreading *L. infantum* to populations of compromised patients. Further analysis of exosome protein and RNA content is currently being conducted using mass spectrometry and RNA-seq analysis at the University of Iowa. We will assess whether exosomes contain circulating proteins and microRNAs from either the host or the parasite that can suppress host immunity and contribute to the pathogenesis of VL to provide targets for new therapeutic approaches. Upon identification of specific targets exosome collection and isolation will be continued in Natal, Brazil.

## Sarah Kottenstette Dr. Resmiye Oral

## Psychosocial Functional Capacities of Children and Their Immediate Caretakers

Experiencing multiple trauma in childhood negatively impacts future health-risk behaviors and health outcomes. Two-generational trauma-informed holistic familycentered family well-being assessment (FWbA) by including the family members' trauma history, resilience, and needs assessment in the diagnostic process was adopted by the UIHC Child Protection Program. An overarching study compared two groups of families evaluated for child abuse and neglect in regard to the documentation and frequency of adverse childhood experiences (ACEs) and service referral rates for children and caretakers. This subsection of the larger study retrospectively reviewed the charts of 364 children in two groups: Post-intervention Group 1: children seen in the child abuse clinic (CAC) in 2014-2016 (received FWbA) and pre-intervention Group 2: children seen in the CAC in 2011-2013. Documentation of ACEs was higher in Group 1 for both children (77.7% vs 26.6%, p<0.0001) and caretakers (60.7% vs 7.3% p<0.0001). Subjects in Group 1 had a higher rate of four or more ACEs for children although not reaching statistical significance (61.4% vs 51.1%, p=0.0571) and for caretakers, which was statistically significant (47.0% vs 5.0% p<0.0001). Conducting TIA in addition to conventional psychosocial evaluation increased diagnostic accuracy for the families evaluated for child abuse and neglect regarding their trauma history. This, in turn, allowed improved case finding for specifically caretakers. Lack of FWbA practice in the evaluation of allegedly abused or neglected children and their families most likely limited the accuracy of diagnostic process and the chance of referrals to needed psychosocial services prior to implementation of FWbA.

## Are College Football Players Who Also Wrestled in High School at a Lower Risk for Concussion than Non-Wrestlers?

Student: Kyle Leubka, M1 Mentor: Andrew Peterson, MD

**Background:** Each year 4 million sports related concussions are suffered in the US [1]. More concussions occur during football than most other sports [2]. In response, much effort has been placed on developing better football helmets in order to soften contact on hits to the head. Helmet technology has improved; however, it does not address the underlying cause of concussions: impacts to the head. Safer helmets may be responsible for risk compensation in football players [3]. A recent study demonstrated that players practicing a helmetless tackling drill saw concussions drop by 28% [4]. We investigated the link between wrestling participation, a physical, non-helmeted sport, and concussion incidence in University of Iowa football players.

**Hypothesis:** A history of wrestling participation in high school lowers concussion risk in University of Iowa football players during their collegiate football career.

## Study Design: Retrospective cohort study.

**Methods:** University of Iowa football players were stratified into those that competed in wrestling and those who did not. High school wrestling participation was obtained from new recruit information packets. Concussion incidence spanning the past 10 seasons was obtained from the University of Iowa Athletic Department's Sports Injury Monitoring System database. Player position, years in the program, and setting of the concussion were also obtained. Generalized estimating equations were used to model the binary outcome of recorded concussion in Iowa football players 2008-2017.

**Results:** A total of 107 concussions were recorded in 83 different players. Most concussions were sustained in practice with 2.37x injuries seen in practice than in games (Practice v Game OR 0.86, 95% Cl, 1.44-1.39). Wrestling participation was not a significant predictor for suffering a concussion with an OR of 0.85 (95% Cl, 0.43-1.68). Player position group wasn't a significant predictor of concussion.

**Discussion:** A history of wrestling participation in high school did not lower concussion risk in University of Iowa football players. These data could be the result of a low sample. More wrestlers and concussion data should be used to test the hypothesis again.

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Developing a Pipeline for Radiomics Biomarkers in Head and Neck Cancer

## Student: Weiren Liu (M2) Research Mentor: John Buatti, MD, Professor and Chair Department of Radiation Oncology

## **Abstract:**

The Quantitative Imaging Network (QIN) is a National Cancer Institute (NCI) funded program that consists of approximately 20 institutions with a central mission "to improve the role of quantitative imaging for clinical decision making in oncology by the development and validation of data acquisition and analysis methods as applied to prediction and response to drug or radiation therapy." The University of Iowa QIN team is working to establish a pipeline for simultaneous analysis of radiomics features generated from head and neck cancer patient PET/CT images using a series of novel and validated tools for image analysis. In previous work, the QIN team established an infrastructure enabling quantitative image analysis tool development and validation as well as their efficient application to outcome prediction tools in clinical trials. This summer research fellowship contributed to the continued development, expansion and analysis within this pipeline. Specifically, datasets of 83 additional head and neck cancer patients were selected, and clinical information with 2 year follow-ups were de-identified, extracted and curated from Epic. The associated PET images are also de-identified but linked via a common identifier to an SQL research database that includes patient and outcomes metadata so all can be linked for decision support system development and testing. Previous validation efforts demonstrated several highly outcome predictive features for H&N cancers that showed persistent uptake at the first post-treatment FDG PET scan using 59 patient datasets. The 83 additional datasets will further validate the tool and provide additional statistical significance. This research is developing a novel integrated platform for precision medicine tools linking radiomics based imaging features with clinical outcomes. This will lead to significant additional publications from this team based scientific endeavor and ultimately may impact the decision making and thereby improve outcome for head and neck cancer patients.

## The Effects of Sleep Quality on Heart Rate Variability in Varsity College Football Athletes

Authors: Will Lorentzen, Carly Day, Andrew Peterson

## **Purpose:**

The purpose of this study was to evaluate the relationship between sleep quality and heart rate variability in NCAA Division I football players.

## Hypothesis:

Athletes who reports poorer sleep quality on the ASSQ will have lower heart rate variability than those who report better sleep quality.

### **Background:**

Heart rate is the average number of heart contractions per minute. Heart rate variability (HRV) measures how much variation in time there is between those beats. HRV is considered a reliable and non-invasive tool to measure physiologic stress [1]. The body responds to physiologic stress through the balance between the opposing branches of the autonomic nervous system, the sympathetic and parasympathetic systems. Stress will increase the activity of the sympathetic system, having many effects on the body including decreasing HRV. Activation of the parasympathetic system has the opposite effect of increasing HRV. For example, physiologic stress such as smoking, history of heart attack, and chronic illness have been shown to decrease HRV [2-4]. Conversely, middle-aged individuals who have maintained good cardiovascular health have greater HRV [5].

Previous research has shown certain sleep disorders lead to lower HRV [5]. These studies have not been done in elite athletes. We were interested in validating these results in athletes because the physiology and sleeping patterns of this group differs from that of the general population. Athletes have been shown to have higher HRV and poorer sleep quality [6, 7].

### Methods:

Quality of sleep was measured through self-reporting. We administered the Athlete Sleep Screening Questionnaire (ASSQ). The Athlete Sleep Screening Questionnaire (ASSQ) is the only sleep survey to have been validated in athletes [9]. It is a 16 question, multiple-choice survey. A Sleep Disturbance Score (SDS) can be calculated from the response. The SDS ranges from 0-17, with a higher number indicating poorer sleep quality.

Athletes provided heart rate variability metrics through the use of the hand-held ithlete device. The football team records and stored heart rate variability metrics on all the players as part of routine training. We obtained consent from the football team to use this data, as well as consent from the individual players. The HRV used for analysis was the mean HRV from the last five days of summer football training camp (7/19/18 - 7/21/18).

The study population consisted of NCAA Division I football players at the University of Iowa. A Pearson Correlation Coefficient was used to analyze the data. A p-value of 0.05 was used to determine significance.

## **Results:**

A total of 104 football players were enrolled. Of those who initially enrolled, 62 players had HRV data that had already been collected by the team. There was no significant correlation between reported sleep quality and heart rate variability in our study.

#### **Discussion:**

We were unable to determine that poorer self-reported sleep led to lower HRV. This is different from previous studies in nonelite athletes. There are several potential mechanisms for this finding, including better overall physical conditioning, increased resiliency, and timing of the study during summer conditioning when other confounding stressors may have been minimized.

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## The Cough is Coming from Inside the House

Mentor: Dr. Alejandro Comellas Presenter: Rob Manges Postdoctoral Researcher: Emma Stapleton, PhD

**Background.** Respiratory infections are the leading cause of acute illness worldwide, and one of the most important causes of death, especially among the very young, elderly, and immunocompromised. Exposure to ambient air pollution is a major risk factor for the development of respiratory infections. An underdeveloped area of research in this field is the health effects of indoor air quality. Research has shown the average North American person spends 80-90% of their life indoors. Indoor air pollution has also been found to increase COPD patients respiratory exacerbations. Prior research by Dr. Comellas' group has demonstrated that outdoor particulate matter (PM) impairs human innate immunity by reducing airway surface liquid (ASL) antimicrobial peptide's function. This research project has built on this prior work and applies the same methodology to examine the effects of indoor air particulate matter. This study seeks to examine the effect of indoor air pollutants on ASL bacterial killing, bacterial growth, and bacterial biofilm formation.

#### Aims.

- 1. To determine the effects of indoor particulate matter on airway surface liquid antimicrobial activity.
- 2. To determine the effects of indoor particulate matter on bacterial growth and biofilm production.

**Methods.** Indoor PM samples were obtained from 21 COPD patients in Johnson county, solubilized in water (1ml H2O per 1 mg of sample), and the soluble portion was used to perform all assays. We assessed PM effects on ASL killing by incubating ASL (from human and porcine explants) with PM, then challenging the ASL with bioluminescent *S. aureus*. A decrease in light production indicates killing by ASL. Bacterial growth was also assessed through bioluminescent *S. aureus*, by comparing the 4 hour growth of S. aureus with PM to the growth of an untreated control. Biofilm production was tested in *Pseudomonas aeruginoas* using a 96-well microtiter plate with an MBEC Calgary lid. Biofilms were established on the lid, then placed in media with the house dust samples for a 24 hour challenge. The lid (with attached biofilms) was stained with Crystal Violet, the stain was eluted, and Optical Density was read as a proxy for biofilm production.

**<u>Results.</u>** Indoor PM appears to affect ASL function, however the effect was variable by the specific house from which the sample was derived. Four houses inhibited ASL killing (altering killing compared to control by > 1SD) and two increased ASL killing. However, when the data was analyzed by comparing COPD exacerbators vs non-exacerbators, the results showed that PM from exacerbators homes inhibited more ASL antimicrobial activity compared to non-exacerbators. Indoor PM increased the bacterial growth in all 21 of the sampled homes, ranging from an increase of120% to 200% of control growth. The effects were variable, but all homes exhibited increased growth in the presence of indoor PM. Biofilm production was also increased across all sampled homes, ranging from 300% to >1500% of the growth of our control. Conversely, in bacterial growth and biofilm production assays, there was no difference between COPD exacerbators and non-exacerbators

**Discussion.** Through these experiments we have demonstrated that indoor PM has an effect on both the function of ASL, and the bacterial growth/biofilm production of *S. aureus* and *P. aeruginosa*. This effect showed variation, especially in the bacterial killing assay, that may reflect physical differences between the homes that were sampled. While there was variability in the magnitude of the effect on bacterial growth and biofilm production, the results showed that the presence of indoor PM correlates to increased growth and biofilm production. The clinical significance of this research is most clear in our analysis of ASL killing by exacerbation status. The results of our analysis indicate that the severity of COPD symptoms may be connected to the makeup of patient's indoor PM. In the future this lab will attempt to determine the extent of the possible effect, and what physical components of indoor PM could be responsible for the variability in growth, ASL killing, and biofilm production.

## Ethical Concerns During the Medical Student Surgical Clerkship

K.A. Marsden<sup>1</sup>, L.C. Kaldjian<sup>3</sup>, E.M. Carlisle<sup>2</sup>; <sup>1</sup>University Of Iowa, Carver College Of Medicine, Iowa City, IA, USA; <sup>2</sup>University Of Iowa, Division Of Pediatric Surgery/Department Of Surgery, Iowa City, IA, USA; <sup>3</sup>University Of Iowa, Carver College Of Medicine/Program In Bioethics And Humanities, Iowa City, IA, USA

**Introduction and Aims:** There is an ever increasing focus on the development of medical school ethics curricula. While much effort has focused on the preclinical years, several groups have worked to identify ethical issues medical students face during their clinical rotations. This work has largely focused on internal medicine, pediatrics, and OBGYN clerkships. Little data is available regarding ethical issues students encounter on the surgery clerkship. Identification of such issues will allow preclinical and clinical course directors to refine ethics curricula to insure students are prepared to address the ethical issues they are most likely to encounter on the surgical rotation. To this end, we performed a content analysis of ethical issues encountered by medical students on a surgical clerkship.

**Methods**: All medical students on the surgical clerkship at a university hospital between April 2017 and June 2018 submitted a written reflection regarding an ethical issue encountered during the clerkship. Two independent investigators performed content analysis of each reflection. References to core ethical principles (beneficence, non-maleficence, justice, autonomy) were tabulated, and ethical issues were classified into 10 main categories and 58 subcategories based on a modified version of a published rubric.

**Results**: 140 reflections were reviewed. 6 were removed due to lack of focus on an ethical issue. 134 reflections underwent content analysis. Non-maleficence was the predominant core ethical principle mentioned, however this was closely followed by justice. Regarding ethical issues, students wrote about challenges with decision making (28%), communication among healthcare team members (14%), justice (12%), communication between providers, patients and families (10%), issues in the operating room (9%), informed consent (9%), professionalism (5%), supervision/student specific issues (5%), documentation issues (1%), and miscellaneous/other (7%).

**Conclusion**: Our analysis identified ethical issues that are of concern to students on the surgical clerkship. Consistent with prior analysis of students on other rotations, our work demonstrates that students express most concern with issues related to decision making. Unlike their peers on other clerkships, surgical students express increased concern with ethical issues surrounding informed consent, communication between treatment teams, and justice. Interestingly, fewer surgical students expressed concern about disrespectful treatment of patients by providers than did students on other clerkships. However, more surgical students expressed concern related to ambiguity about their role/responsibility on the surgical team, as well as the challenge of balancing delivery of efficient yet high-quality care. Integration of these specific ethical concerns into preclinical and clinical ethics curricula may help prepare medical students for the ethical issues that they will encounter on the surgical clerkship.

#### Outpatient Frailty as a Risk Factor for the Development of Delirium in Geriatric Inpatients

Marissa Martin<sup>1</sup>; Korey Kennelty PharmD, MS, PhD<sup>1,2</sup>; Jose Monestina<sup>3</sup>; Yinghui Xu MS<sup>3</sup>; Michelle Weckmann MS, MD<sup>1</sup>; Nicholas Butler MBA, MD<sup>1</sup>

<sup>1</sup>University of Iowa Roy J. and Lucille A. Carver College of Medicine, Iowa City, Iowa; <sup>2</sup>University of Iowa College of Pharmacy, Iowa City, Iowa; <sup>3</sup>University of Iowa Hospitals and Clinics, Iowa City, Iowa

**BACKGROUND:** Frailty and delirium commonly coexist in geriatric patients. Both syndromes have been independently associated with patient decline, particularly when they are observed in the time period surrounding a hospital admission. Frailty is a state of diminished physiological functioning and impaired homeostatic mechanisms that make an individual more susceptible to the morbidity and mortality associated with common illnesses and injuries. Past studies have estimated the prevalence of frailty to be as high as 59% among older adults living in the community and 80% among hospital inpatients. Delirium is a fluctuating disturbance in consciousness with an acute onset of symptoms that can include confusion, disorientation, hallucinations, and agitation. It has been shown to occur in up to 56% of general geriatric inpatient stays and 80% of critically ill patients, many of which are geriatric. Delirium is well known to increase rates of mortality, with one study demonstrating that 35.9% of patients with delirium died during their initial admission compared to only 6.9% of patients without delirium who died. Initial data on the relationship between frailty and delirium suggests that frail elderly patients who develop delirium. The morbidity and mortality of frailty and delirium, particularly when they occur together, makes understanding these two syndromes, exploring their connection, and investigating their co-occurrence in the time period surrounding hospital admissions clinically important.

**OBJECTIVE:** To determine if frailty assessments of geriatric individuals done in the outpatient setting correlate with the likelihood of these individuals developing delirium in the inpatient setting.

**DESIGN:** IRB-approved retrospective cohort study.

SETTING: University of Iowa Hospitals and Clinics.

**PARTICIPANTS:** Individuals who had an outpatient geriatric clinic visit with a recorded frailty assessment preceding an inpatient admission with a recorded delirium assessment between June 1, 2014 and May 1, 2018. The most recent admission for each participant was included regardless of reason for admission or admitting service.

**MEASUREMENTS:** Data collected via medical record abstraction for each patient included The Fried Frailty Phenotype score (scored 0-5 with 0 indicating non-frail, 1-2 indicating prefrail, and 3-5 indicating frail), the Delirium Observation Screening Scale (DOSS) score (scored 0-13 with 3 or higher indicating delirium), the presence of diagnoses included in the Charlson Comorbidity Index (CCI) or deemed potentially influential in the development of frailty or delirium, and the use of medications that contribute to the anticholinergic burden (ACB) score (a higher score indicates a higher anticholinergic burden).

**RESULTS:** 126 patients were identified. The patient population was 64% female (n=81), 94% white (n=118), and 37% married (n=47). Participants' average age was 83.2 years ( $\pm$ 7.8, range 66-98 years). The median DOSS score was 1 (range 0-12) and median frailty score was 2 (range 0-5). The Spearman Correlation Coefficient correlating DOSS scores and frailty scores was r=0.28. The median CCI score was 5 (range 0-18) and the median ACB score was 1 (range 0-6).

**CONCLUSION:** In this geriatric population, outpatient frailty had a weak positive correlation with the development of inpatient delirium. The positive correlation indicates that a higher degree of frailty is associated with an increased incidence of delirium. However, the weakness of this relationship suggests it may be beneficial to consider other factors in addition to frailty when assessing a patient's risk for developing delirium. Further analysis of the data to determine how patients' baseline health (as depicted by CCI score), other medical diagnoses, or use of anticholinergic medications (as demonstrated by ACB score) impacted this finding is underway now.

## Academic Achievement of Iowa Children with Brain Tumors

Hannah McAtee, Sheila Barron, Amanda Grafft, Timothy Ginader, Charles Lynch, Mariko Sato

**ABSTRACT:** The purpose of our study is to identify whether children with brain tumors had academic impairment prior to diagnosis as well as to examine longitudinal trends of academic achievement prior to and after the treatment, by utilizing two state-wide databases: The Iowa Testing Program (ITP) and Iowa Cancer Registry (ICR). The ITP uses a set of standardized academic achievement measures, the Iowa Assessments, designed for students from kindergarten through high school, while the ICR has records of patients with brain tumor diagnoses since 1973.

A deterministic linkage of the ICR and ITP databases was performed to identify 589 children with brain tumors who performed Iowa Assessments between 2000-2016. These patients were diagnosed between 0 and 20 years of age; median age at diagnosis was 9 years old, and 212 children had Iowa Assessments done prior to diagnosis. Achievement data, in the form of percentile rank scores by grade and content domains (e.g., reading, mathematics) were analyzed.

There was no significant academic impairment identified prior to diagnosis however math computation level was lower than other domains prior to diagnosis. Comparison of academic achievement prior to and after diagnosis revealed significant academic decline in both benign and malignant tumor groups. There was no significant difference in score trajectory between different treatment regimens after diagnosis in our cohort.

This is the largest population-based study for academic achievement in children with brain tumors. There is a need for prospective study of academic achievement to further identify vulnerable populations who may develop academic impairment.

## Quantifying Functional Disability in Individuals undergoing Periacetabular Osteotomy for Hip Dysplasia

Arthur Mercado, Elizabeth Scott, Eric Sorensen, Jason Wilken, Michael Willey

## Introduction:

Physical performance measures (PPMs) provide an attractive alternative to patient-reported outcome instruments (PROs) in the non-arthritic hip. We evaluated the reliability and patient perception of four simple physical performance measures in young adult subjects with hip dysplasia undergoing periacetabular osteotomy (PAO).

## Purpose:

Specific Aim: Validate the use of objective physical performance measures and patient-reported outcome instruments including the hip disability and osteoarthritis outcome score (HOOS), international hip outcome tool (iHOT), and PROMIS Physical Function Computer Adaptive Test (PROMIS-PF CAT) in patients with symptomatic hip dysplasia, and characterize the degree of disability in patients prior to surgical treatment.

Hypothesis: Physical performance measures and PROs will be valid in comparison to standard accepted patientreported outcomes (mHHS), and that patients will demonstrate substantially decreased function in comparison to healthy age-matched controls prior to PAO.

## **METHODS:**

Fifteen individuals age 14-39 years indicated for PAO completed PROMIS PF-CAT, iHOT-12, HOOS-PS and HOOS-PAIN, mHHS, and VAS for pain, as well as four simple physical function tests including the (1) Timed Stair Ascent (TSA), (b) Self-Selected Walking Velocity (SSWV) test, (c) Four-Square Step Test (FSST) and Sit-to-Stand Five Times Test (STS5). PPMs were also completed by seventeen asymptomatic adults of similar age as controls.

## **RESULTS:**

Patients with dysplasia demonstrated significant decrements in performance of all tested physical measures compared with asymptomatic controls (CON vs DYS, SSWV: 2.47 vs 1.95 m/s, p = 0.002; TSA 3.36vs 3.80 s, p = 0.054; FSST: 4.12 vs 5.52 s, P <0.001; STS5, CON 10.3 vs 6.10 s, p < 0.001) (Table 1). Activities involving lower extremity strength and dynamic balance (FSST, STS5) were most strongly associated (r >0.67, p <0.001, r >0.44, p<0.001) with increased reports of disability on the iHOT-12.

## **CONCLUSION:**

Hip dysplasia has a negative affect on objectively measured physical function. Hip-specific measures including FSST and STS5 are able to detect dysplasia-associated disability and may be used to objectively assess surgical or rehabilitative outcomes.

	Hip Dysplasia	Asym. Controls	
	N = 15	N = 17	P Value
Female	14 (83%)	14 (82%)	NS
	Avg (Min-Max) St Dev	ev Avg (Min-Max) St Dev	
BMI (m/kg2)	23.54 (17.5 – 36.6) 5.47	24.34 (20.2 – 33.1) 3.43	NS
Age (years)	25.0 (14.0–39.0) 10.6	25.1 (18.0-39.0) 6.86	NS
Weekly Opioid Use	3 (20%)	0 (0%)	
Physical Performance Measures (PPMs)	Avg (Min-Max) St Dev	Avg (Min-Max) St Dev	P Value
SSWV (m/s)	1.95 m/s (3.90-7.64) 1.07	2.47 m/s (2.97-4.9) 0.59	0.002
TSA (s)	3.81 (2.79 – 6.04) 0.79	3.36 (2.67-3.88) 0.30	0.054
STS5 (s)	10.31 (6.36 – 10.31) 2.91	6.10 (4.77 – 9.22) 1.18	<0.0001
4SST (s)	5.52 (3.56 – 7.88) 1.19	4.12 (3.13 – 5.56) 0.68	<0.0001

**Table 1**. Demographics and performance of PPMs for both dysplastic individuals and asymptomatic controls

## SOCIAL DETERMINANTS OF HEALTH NEEDS ASSESSEMENT WITHIN AN INPATIENT POPULATION AT UIHC

Katherine Merritt, MS<sup>1</sup>, Kevin Glenn, MD, MS<sup>2</sup>

<sup>1</sup>University of Iowa Carver College of Medicine, Iowa City, IA

<sup>2</sup>Department of Internal Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA

## BACKGROUND

In the current state of healthcare, health systems are focusing on the Triple Aim: reducing readmission rates and improving care, while simultaneously reducing costs. One way that health systems are tackling this issue is by addressing the social needs that affect a patient's overall health. These social needs, known as social determinants of health (SDoH), have been shown to contribute twice as much to a person's overall health than healthcare itself. Initiatives at University of Iowa Hospitals and Clinics (UIHC), such as the Upstream Clinic, have begun integrating SDoH with patient care. In an initial survey done by the Upstream Clinic within the Perinatal Diabetes Program (PDP) at UIHC, 40% of patients identified at least one social need related to food insecurity or transportation. However, outside of the Upstream Clinic, there is a lack of data and very few interventions regarding SDoH at UIHC.

## **OBJECTIVE**

The primary objective of this study is to identify the most common social needs amongst the General Internal Medicine (GIM) inpatient population at UIHC and analyze these needs based on patient demographics, especially in regard to rurality of a patient's hometown.

## **METHODS**

Data for this study was gathered from two sources. First, patients on the UIHC General Internal Medicine unit (6RC) were identified via EPIC based on their county and its status of rurality as designated by the Office of Management and Budget. Demographic data was collected from these patients, including, but not limited to, whether or not the patient had an established primary care physician, insurance status, and zip code. Second, these patients were surveyed for self-identified social needs using validated questions from the Health Leads Social Needs Screening Tool. Data was analyzed via IBM SPSS to determine the percentage of patients identifying at least one social need in addition to the top needs identified. The data was then stratified by demographics using logistic regression to identify the impact of each variable on whether or not a patient identified a social need.

#### RESULTS

Data analyzed with descriptive statistics revealed that 54.4% of patients (n=57) indicate a social need. Of these, 64.5% of patients were from a rural county, which significantly correlated with indication of at least one social need (CI = 1.15-10.23). The top identified social needs include: job insecurity (24.6%), housing insecurity (21.1%), issues with transportation to medical appointments (21.1%).

## CONCLUSION

More than half of the patients on the General Internal Medicine unit (6RC) at UIHC indicated at least one social need. It is important that the health system understands their patient's needs outside of a medical setting since social factors have such a large impact on overall health. Additionally, it is important to consider the environmental and access barriers that a patient encounters, which may be intensified by the rurality status of a patient's hometown. This information should be used to spread awareness of the social needs of patients at UIHC and as a starting point for SDoH initiatives at UIHC. Focusing on SDoH has been shown to lead to reduced readmissions and increased patient satisfaction. In order for UIHC to continue being a leader in healthcare, it is important to listen to and act upon social needs as they directly correlate with health outcomes of our patient population.

#### **Insights into Arch Vessel Development in the Bovine Aortic Arch**

Alex M. Meyer, BS, Joseph W. Turek, MD, PhD, Julia Froud, BS, Levi A. Endelman, BA, Nicholas B. Cavanaugh, BS, Jose E. Torres MD, Archana T. Laroia, MD, Ravi Ashwath, MD

**Objectives:** A bovine arch is the most common variation of aortic arch branching and is characterized by the innominate artery and the left common carotid artery sharing a common origin or the left common carotid artery arising from the innominate artery. Although believed to be a normal variant, data has shown that children with bovine arch anatomy and coarctation are at a significantly higher risk of re-coarctation following extended end-to-end anastomosis via posterolateral left thoracotomy. This study aims to assess the branching of the arch vessels, understand their embryologic origins, and delineate their patterns of displacement of the arch vessels in bovine versus normal anatomy.

**Methods:** In this retrospective study, the medical records of 178 infants (<1 year old) who had a chest computed tomography (CT) scan with contrast (CTA) (58) or CT scan without contrast (120) at our institution between 2007 and 2017 were reviewed. Multi-planar reconstruction (MPR) software built into CareStream<sup>®</sup> was used to obtain the best image plane to display the sinotubular junction (STJ), innominate artery, left common carotid (LCCA), and left subclavian arteries (LSCA). We measured HV1, the distance from the STJ to the midpoint of the innominate artery; HV2, the distance between the midpoints of the innominate artery and the LCCA; and HV3, the distance between the midpoints of the LCCA and LSCA. In the bovine arches, HV2 was measured as 0.0 mm. All distances were standardized to body surface area (BSA) and STJ diameter, which is a novel method.

**Results:** Bovine arches were found in 32.6% of the patients. The total arch length of both arch anatomies was similar. HV3 is longer in bovine arches. HV1+HV2 and HV2+HV3 are longer in the normal arches than the bovine arches.

**Conclusions:** The LCCA moves proximally to join the innominate artery with statistical significance in the formation of the bovine arch. The innominate artery moves distally ever so slightly without statistical significance. Aortic arch distance standardized to STJ diameter produced similar results when compared to the aortic arch distances standardized to BSA.

## The role of the inflammasome in generating CD8 T cell responses and protection against malaria

Maddie Mix<sup>1</sup>, Sam Kurup<sup>2</sup>, Mitchell LeFebvre<sup>1</sup>, Lecia Epping<sup>2</sup>, John Harty<sup>1,2,3,4</sup>

<sup>1</sup>Medical Scientist Training Program, University of Iowa, Iowa City, IA <sup>2</sup>Department of Microbiology and Immunology, University of Iowa, Iowa City, IA <sup>3</sup>Department of Pathology, University of Iowa, Iowa City, IA <sup>4</sup>Center for Immunology and Immune-Based Diseases, University of Iowa, Iowa City, IA

**Background:** Malarial disease has an immense global burden, with nearly 200 million annual infections and over 40% of the world's population at risk of infection. *Plasmodium* species, which serve as the causative agent of malaria, travel to the liver after infection for an essential replication stage. Upon progression into blood-stage malaria, parasitized erythrocytes can become sequestered in the brain microvasculature to induce fatal cerebral malaria. While vaccination strategies such as immunization with radiation attenuated sporozoites (RAS) have generated protective memory CD8 T cell responses against *Plasmodium*, sterilizing immunity remains to be achieved. Until recently, the role of the innate immune system in detecting fulminant *Plasmodium* infection had been understudied. However, our group has identified that knock-out (KO) mice which lack canonical inflammasome signaling present with increased liver parasite burden upon a primary *Plasmodium* challenge. This project aims to define, in vaccination or challenge settings, whether innate inflammasome mediators are required to generate CD8 T cell responses and protection during liver-stage and blood-stage malaria.

**Methods:** Ubiquitous KO mice on the C57BL/6 background were employed for the following inflammasome mediators: AIM2, NLRP3, ASC, and Casp1. *Plasmodium* prime-boost immunization was conducted through sequential intravenous injections of *P. yoelli* or *P. berghei ANKA* RAS. Following *Plasmodium* challenge, liver-stage malaria analysis was conducted at 44 hours post-infection while blood-stage malaria analysis began at 7 days post-infection.

**Results:** In RAS prime-boost immunization strategies, *Plasmodium*-specific circulating CD8 T cell responses were significantly impaired in inflammasome KO mice compared to WT mice. Furthermore, hepatocyte RT-qPCR analysis for parasite burden revealed that singly immunized AIM2 KO mice were less protected than their WT counterparts following *Plasmodium* challenge. Interestingly however, despite similar levels of parasitemia, inflammasome KO mice upon blood-stage malaria induction.

**Conclusions:** This work may highlight the duality of immune responses stimulated by inflammasome signaling in the context of malarial stages. Hepatocyte parasite clearance may be achieved through protective inflammasome responses while immunopathology and mortality later ensue due to inflammasome action at the blood-brain barrier. Further studies are necessitated to delineate whether inflammasome involvement is critical in hepatocytes or cells of the neurovascular unit for these respective experiments. Nonetheless, this work recognizes the inflammasome as a robust pathway of detecting *Plasmodium* infection to stimulate CD8 T cell responses and may therefore influence adjuvant selection in future immunization strategies.

# Treating heart failure in Duchenne muscular dystrophy: is proactive better than reactive?

## Authors:

Cassandra B. Moylan, BS, Colton G. Brown, BS, Jennifer R. Maldonado, BS, RTR, R. Erik Edens, MD, PhD, Katherine D. Mathews, MD, Ravi C. Ashwath, MD

## **Abstract:**

**Background:** Duchenne muscular dystrophy (DMD) is an x-linked childhood muscular dystrophy. Cardiomyopathy is a major cause of morbidity and mortality. Mean age of heart failure (HF) onset in DMD is 14.3 years (1). HF medications (HFM) are often initiated at HF onset. However, evidence for a cardioprotective effect of HFM has led to the recent recommendation for initiation before onset of HF.

**Objective:** To determine if prophylactic initiation of HFM delays onset of HF in DMD. **Methods:** Retrospective review of DMD patients allowed classification into prophylaxis group (PG) or treatment group (TG) based on whether HFM was initiated before or after evidence of HF, defined by ejection fraction (EF) <55% or fractional shortening (FS) <28%. Age at start of HFM, specific HFM, EF and/or FS at or before start of HFM, and age at HF onset were collected. Mean values were compared using two-sample Mann-Whitney U or Z-test. **Results:** 104 subjects (77 PG and 27 TG subjects) were included. Mean age in years at start of HFM in the TG was 17.8 (95% CI, 15.9-19.8) and 10.8 (95% CI, 10.0-11.7) in the PG (p < .0001). Forty-seven (61%) PG subjects are alive without HF; mean age at last visit was 13.5 (95% CI, 11.9-15.1). PG subjects (n=23) developed HF at 18.1 (95% CI, 16.0-20.2) years, TG (n=27) at 17.8 (95% CI, 15.9-19.7) years. HF onset was later than reported by Barber et al. (P < .001), but there was no difference in HF onset between TG vs. PG (Table 1).

**Conclusions:** In our cohort, prophylactic initiation of HFM in DMD did not alter age at HF onset, however most of our PG subjects are currently alive with normal EF and are younger than the mean age at HF onset. Continued follow up of this population will clarify if cardiac prophylaxis delays HF.

## **References:**

1. Barber, B.J., et al., *Oral Corticosteroids and Onset of Cardiomyopathy in Duchenne Muscular Dystrophy.* The Journal of Pediatrics, 2013. **163**(4): p. 1080-1084.e1.

Group	Number of subjects	Mean age at start of HFM	95% CI (+/-)	Mean age at HF onset	Mean age at last visit	Mean age at death	95% CI (+/-)
Barber et al.	202			14.3			0.579
TG	27	17.8	1.934	17.8			1.934
PG	77	10.8	0.856				
Subgroup of PG							
PG with HF	23	13.1	1.26	18.1			2.078
PG without HF	47	9.2	0.947		13.5		1.628
PG deceased prior to HF	7	14.1	2.808			19.9	2.206

**Transplantable photoreceptor grafts from patient-specific pluripotent stem cells.** Nathaniel K. Mullin (M1G) Laboratory of Budd Tucker, PhD Department of Ophthalmology and Visual Sciences Institute for Vision Research

Genetic disease specifically effecting the photoreceptor cells of the retina can lead to vision loss and blindness. Establishing a production strategy for these post-mitotic cells would create a therapeutic option for those patients whose photoreceptor cells have died. Since the advent of induced pluripotent stem cell (iPSC) reprogramming technology a decade ago, easily obtainable somatic cells (skin fibroblast, peripheral blood cell, etc.) have become a viable starting material for the production of autologous photoreceptor cells. We have designed a reprogramming and *in vitro* differentiation strategy that allows for prototyping of such transplantable photoreceptor grafts. iPSCs derived from patient dermal fibroblasts using nonintegrating vectors are converted to neural/retinal progenitor cells through an established embryoid body driven protocol. In order to mimic in vivo development and generate a transplantable unit of cells, biodegradable 3D-printed structures are used to house differentiating cells. Such structures can be rapidly designed and printed using an in-house twophoton 3D lithography printer. Before the addition of cells, structures can be assessed for structural integrity using confocal microscopy and automated image analysis of various designed features. Cells are seeded onto optimally-designed structures, and their maturation is monitored on the basis of expression of known retinal marker Otx2. iPSC-derived retinal progenitors appear to integrate into and proceed to develop within 3D-printed scaffolds as evidenced by Otx2+ nuclei present in the scaffold after 9 days of maturation. The pipeline described here will allow for the improvement of our differentiation strategy, enabling the production of iPSC-derived photoreceptor grafts for clinical use. Further, this strategy of combining synthetic scaffolding with patient-specific iPSC-derived cells will allow for a better understanding of the differentiation dynamics and disease processes of the retina.

## A Survey of American Tegumentary Leishmaniasis in the Endemic Region of Corte de Pedra, Bahia, Brazil

Marcus Muñoz, Bruno Cova, Lilian Medina, Juliana Almeida Silva, Paulo Machado, Albert Schriefer, Edgar Carvalho, and Mary E. Wilson

Medical Student Research Conference August 27, 2018

*Leishmania (Viannia) braziliensis* is a parasite that causes American tegumentary leishmaniasis (ATL) and is transmitted by the bite of a phlebotomine sand fly of the genus *Nyssomyia*. ATL is a chronic, ulcerating, infectious disease. In the Corte de Pedra region in the state of Bahia, Northeast Brazil, *L (V.) braziliensis* causes a range of clinical presentations: localized cutaneous leishmaniasis (CL), mucosal leishmaniasis (ML), and disseminated leishmaniasis (DL). Our collaborators at the Federal University of Bahia (UFBA) study many aspects of the parasite life cycle and pathogenesis: vector borne transmission, clinical treatment trials, patient immune responses, and parasite genomics and proteomics. These studies require clinician scientists to travel to endemic regions of the state, examine and collect diagnostic biopsies from infected subjects, isolate *Leishmania* spp. isolates from patients, and collect sand flies from the homes of patients with disease. The goal of this summer project was to participate in collection of samples, observe the ongoing clinical treatment trials of the various forms of ATL, and help monitor *Phlebotomus* spp. vectors near patient households in the Corte de Pedra region.

#### Parasite quantification in biopsies by qPCR of genomic DNA

Parasite load may play a role in the pathogenesis and treatment outcomes of different forms of ATL in the region. Punch biopsies were collected from lesion borders under local anesthesia for diagnostic cultures and histology. Leftover tissue available for research was immersed in DNA extraction buffer. Parasite genomic DNA was isolated from biopsy using Wizard® Genomic DNA Purification Kit. DNA was then analyzed via qPCR for presence of, and quantification using kDNA3, a specific marker for *L*. (*V*.) *braziliensis*. Due to melt curve abnormalities and difficulties in obtaining reproducible standard curves, parasite load data from this experiment was inconclusive. Moving forward we plan to optimize the DNA extraction and qPCR protocols to improve these results.

#### Macrophage binding of parasite isolates Analysis

The GP63 surface protein of leishmaniasis has been shown to be integral to the parasite attachment, internalization, and survival. The group has identified distinct clades of *L. (V.) braziliensis* associated with different clinical forms of ATL. These can be identified by polymorphisms in GP63 domains. We examined the hypothesis that different clades will bind differently to human macrophages. Therefore, 4 synthetic peptides corresponding to domains of GP63, HEVAH, SRYD, PAVGNIPA, and KAREQYGC were synthesized, and tested in macrophage binding inhibition assays. The percent of macrophages infected and the number of parasites/infected macrophage were recorded. Although preliminary, the data suggests that each synthetic peptide decreased the proportion of infected macrophages as compared to negative control. However, no trends were found when observing the number of parasites/infected macrophages as compared to control. Future studies will work to strengthen this data and identify the presence of these domains in patient isolates from the region.

#### **Phlebotomine Sand Fly Collection**

The proportions of infected sand flies in different environments are under study. To collect sand flies, CDC Mini Light traps were set near households of patients recently diagnosed with ATL. Per household, three traps were set: one within the household, one within a 50 meter radius of the household outside, and one in the surrounding sylvatic environment. Traps were set at dusk and collected at dawn. Humidity levels and GPS coordinates for each trap were recorded. The collected insects were sorted and stored in 70% ethanol, and species were identified by morphology under a dissecting light microscope. 9 different species of sand flies were isolated from the 3 different houses. The two primary vectors for leishmaniasis in the region, *Nyssomyia intermedia* and *Nyssomyia whitmani* were observed in all three houses, while a secondary vector of the region, *Migonemyia migonei*, was observed at only one house. Collection of *Phlebotomus* spp. sand flies will continue throughout the next year and future studies will be conducted to determine various mammalian hosts of leishmanial parasites in the region.

## Mental Health and Substance Abuse Patients in the Emergency Department: Mobile Crisis Outreach and Healthcare Utilization.

Ryan Neuhaus, MS; Brittany Griffin, PhD; J. Priyanka Vakkalanka, ScM; Sangil Lee, MD, MS.

**Background**: Mental Health and Substance Abuse (MHSA) patients in the emergency department (ED) have been facing increasing lengths of stay due to a shortage of inpatient beds. Mobile Crisis Outreach (MCO) has the potential to reduce long ED stays for MHSA patients by providing de-escalation and mental health evaluation, and by connecting MCO users to community resources providing longer term stabilization. Our objective was to describe the healthcare utilization of those who had access to the MCO program.

**Methods**: We performed a retrospective chart review of 14 months of MCO encounters from one organization that serves two counties of a Midwestern state. We limited records to the first MCO encounter and reviewed one hospital's ED records for potential encounters within six months of the MCO encounter. We quantified demographic (i.e. age, race/ethnicity, sex, insurance status, homelessness, veteran status, and history of crime victimization), reported mental health conditions (e.g. depression, psychosis, substance abuse), and current medications. We evaluated potential lethality at the beginning and end of each encounter [(scale of 1 (minimal/limited crisis) to 5 – (profound crisis)], follow-up plans and referrals recommended by the MCO specialist, and the extent to which the ED was utilized.

**Results**: Of the 185 clients, 51% were females and the mean age was 36 years. Additionally, 68.6% were Caucasian and 15.1% were African American. MCO users most commonly had depression (60.0%), suicidal ideation (56.2%), and anxiety (49.7%). Approximately 44% of patients reported previous suicide attempts. MCO staff were able to significantly reduce their client's lethality level by an average score of score of 1.5 (95% CI: 1.4-1.6). Eleven percent of patients (11.4%) were referred to the ED. Within 6 months of the MCO encounter, 69.7% of patients had at least one ED visit and 40.5% had at least two visits (range: 1-31).

**Conclusion**: MCO has the potential to reduce overcrowding and ED wait times by stabilizing the crisis on site and referring clients to other resources. More research needs to be done to see if ED utilization decreases following MCO encounters, and to see if MCO usage affects patient risk for adverse effects such as suicide attempt or overdose.
Title: Impacts of Enhanced Recovery After Surgery Pathway on Length of Stay, 30-day Mortality Rate, and Complication Rates in Transhiatal Esophagectomy Patients

**Presenter:** Lucas Nguyen, M4 **Mentor:** John Keech, MD

**Purpose.** Esophagectomy is a common operation performed for esophageal cancer that can have a prolonged LOS and high morbidity. We recently instituted a standardized post-operative enhanced recovery after surgery (ERAS) pathway after transhiatal esophagectomy. We sought to compare the impact of our ERAS pathway and the pre-ERAS patients.

**Methods.** A retrospective review from our single-institution database of patients who underwent a transhiatal esophagectomy was performed. Between 2008 and 2018, there were a total of 284 patients who underwent a transhiatal esophagectomy; 150 of them received our ERAS pathway (standardized pain and therapy regimen, chest tube and tube feed management, and delayed oral intake) and 134 were in the pre-ERAS group. The mean LOS, 30-day mortality rates, and complication rates (anastomotic leak, chyle leak, anastomotic stricture, aspiration, and recurrent nerve injury) between two groups were calculated and analyzed using multiple paired t-tests and chi square tests.

**Results.** The mean LOS of the ERAS and pre-ERAS groups were 9.95 and 7.85 days, respectively (p = 0.03). The 30-day mortality rate in the ERAS and pre-ERAS groups were 2.04% and 2.99%, respectively (p = 0.61). The complication rates are listed in table 1. There is no statistically significant in these complication rates in the two groups.

**Conclusions.** After instituting an ERAS pathway, there was no significant difference in 30-day mortality rate and complication rates, but we did notice a significant difference in LOS by over two days favoring the ERAS patient group. Our ERAS pathway following transhiatal esophagectomy is safe and results in a shorter hospital stay.

Complication	ERAS rate (%)	Pre-ERAS rate (%)	<b>p-value</b> 0.47	
Anastomotic leak	6.72	7.28		
Chyle leak	2.99	1.32	0.49	
Anastomotic stricture	8.96	3.97	0.22	
Aspiration	12.69	7.95	0.51	
Recurrent nerve injury	3.73	2.65	0.87	

**Table 1.** Complication rates between ERAS and pre-ERAS groups.

## Activation and Utilization of an Electronic Health Record Patient Portal at an Academic Medical Center - Impact of Patient Demographics and Geographic Location

Sarah E.R. Oest, Maia Hightower MD, Matthew D. Krasowski MD, PhD

## Background

Electronic health records (EHRs) are common in industrialized countries and provide a way to store patient health information in a secure, efficient, and easily accessible manner. Online EHR portals are a tool for increasing patient engagement and high value care, and have become increasingly prevalent in recent years. Previous literature has revealed that EHR portal usage patterns differ depending on patient demographics; active users tend to be Caucasian, younger, female, English-speaking, and have fewer medical problems than non-users. However, usage patterns by race and geographic location are underreported in the literature.

## Purpose

In this report, we analyze how demographic variables including race, geographic location, age, and gender affect patient portal activation and usage at the University of Iowa Hospitals and Clinics. Our primary endpoints were activation of the patient portal (MyChart, Epic, Inc.) and access of outpatient laboratory and radiology results, which are among the most commonly accessed features of the patient portal. The aim of this study is to identify disparities in online health portal usage, in addition to highlighting those that have been previously described.

## Methods

This project had IRB approval as a retrospective study. We analyzed data from 536,378 patient encounters to determine rates of patient portal activation, and data from 219,671 patient encounters to determine the frequency at which patients access their online diagnostic test results. Patient data was organized based on age, gender, race, distance from UIHC, and city size (Metropolitan, Micropolitan, or Rural), and analyzed using Microsoft Excel. Epic Reporting Workbench (RWB) was used to retrieve patient demographics, MyChart status, pathology results, and radiology reports covering dates from October 1, 2016 to October 1, 2017.

## Results

Higher rates of EHR portal activation were associated with female gender, Caucasians/nonunderrepresented minorities, geographic location in closer proximity to the medical center (Iowa City and neighboring cities/suburbs), and non-elderly adults. Patients with the lowest likelihood of activating their EHR portals include elderly adults, African American and Hispanic Patients, and patients living in a rural setting. Underrepresented minorities, elderly adults, and rural patients also had lower rates of portal usage than the other demographic groups, however, the percentage gaps between low and high activity users were less pronounced than the gaps between activation rates.

## **Conclusion/Discussion**

Possible explanations for low EHR portal activation and usage include limited access, low health literacy, and barriers to the English language, among others. Our data suggests that activation of the EHR portal account is a significant barrier in differences between sub-groups of patients. Once patients have active accounts, they are more likely to use their patient portal, at least as it pertains to outpatient diagnostic test results. More research should be done to determine how to minimize these discrepancies in patient portal usage and increase access to underserved populations.

## Nutritional Composition of Diet in Individuals with MS following a Multimodal Intervention

Michael Orness, Babita Bisht PhD, Terry Wahls MD

## Introduction

Multiple sclerosis (MS) is a degenerative disease of the central nervous system that affects around 400,000 people in the US. The cause of MS is complex, but is believed to be an immune-mediated disease. Currently, genetic and environmental factors are proposed etiologies for MS. Researchers have found that almost 74% of MS patients experience fatigue, which has been shown to be one of the most debilitating symptoms. Non-pharmaceutical interventions have shown promise in reducing fatigue. Previously, we reported beneficial effects of a multimodal intervention (modified Paleolithic diet, stretching and strengthening exercises of trunk and lower limb muscles, neuromuscular electrical stimulation and stress reduction techniques) on fatigue and quality of life in subjects with progressive MS. Now we report the nutritional content of the modified Paleolithic study diet. We analyzed the change in macronutrient and micronutrient content of the diet in study participants from baseline to 12 months and assessed whether a change in nutrient intake was associated with changes in clinical outcomes.

## Methods

Nineteen individuals with progressive MS (mean age 51.5; SD, 6.6) years participated in this study. Nutrient intake of study participants was determined using the 2007 Harvard semiquantitative food frequency questionnaire. Participants completed this questionnaire at baseline and 12 months. The survey asked how frequently each food item was consumed per day, week, month, or year. Responses were used to calculate the average daily intake of nutrients. We assessed change in intake of important nutrients from baseline to 12 months using paired t-test for normal data and Wilcoxon rank test for non-normal data. We also assessed the relationship between change in nutrient intake and change in fatigue and quality of life using Spearmen's correlation. For this analysis we included nutrients and clinical outcome measures which showed significant change over 12 months.

## Results

Study participants showed significant decrease in average daily calorie intake (-522 kcal, p=0.002) from baseline to 12 months. On average, percent daily calorie intake from carbohydrates (-11.7 kcal), saturated fats (-2.7 kcal) and added sugars (-7.2 kcal) decreased whereas percent calorie intake from protein (+5.4 kcal) and total fat (+9.2 kcal) increased (all p<0.003). Average intake of dietary fiber (4g) and linolenic acid (+0.8g) increased and glycemic index and glycemic load decreased (all p<0.025). Change in average daily intake of vitamins and minerals was assessed with and without supplement use. From only food sources, average intake of vitamin A RAE, vitamin C, vitamin K, vitamin B12, and copper increased. However, intake of vitamin B1, iron, calcium, and sodium decreased. When including supplement use in the analyses, vitamin A RAE, vitamin C, vitamin K, vitamin B2 and vitamin B12 increased and glycemic index and glycemic load decreased. These results indicate that, on average, study participants made healthier food choices and increased nutrient density of their food. We did not find any significant correlation between changes in nutrient intake and changes in fatigue or quality of life measures.

## Conclusion

Individuals with progressive MS who followed a modified Paleolithic diet as part of a multimodal intervention showed significant decrease in their daily calorie intake. Adherence to the diet resulted in decreased intake of carbohydrates, saturated fats and added sugars, suggesting healthier food choices. Additionally, this diet resulted in increased intake of several important vitamins and minerals. Both glycemic index and glycemic load of diet decreased from baseline to 12 months.

## Characterization of a small peptide in INS-1 832/3 Pancreatic Beta Cells

Daniel Pape, Mark Li, Qingwen Qian, Huojun Cao, Ling Yang

Introduction: Currently, diabetes afflicts almost 1 of every 10 adults worldwide, with type II diabetes accounting for 90-95% of cases. Insulin is produced by beta cells, which are found in the endocrine tissue of the pancreas called the islets of Langerhans. In the pre-diabetic state, when the peripheral tissues are slowly becoming insulin resistant, the beta cells help maintain normoglycemia by producing more insulin. However, this increased insulin demand stresses the beta cells and ultimately leads to beta cell failure and death. This causes the onset of full type II diabetes. While this process has been studied extensively, there remains a lack of knowledge on the molecular mechanisms governing beta cell function and their failure in type II diabetes. Recently, using bioinformatics techniques, we identified a small peptide ("B-peptide") expressed in beta cells that might play an important role in regulating insulin secretion and overall beta cell function.

<u>Purpose</u>: The purpose of this study was to investigate whether B-peptide modulates insulin secretion from beta cells. If so, what is the mechanism? We sought to answer three questions: First, where does B-peptide localize in the cell? Second, does B-peptide modulate insulin secretion? Third, does B-peptide enhance intracellular calcium flux in the beta cell?

<u>Methods</u>: To investigate the function of B-peptide, we generated N-terminus and C-terminus B-peptide constructs tagged with FLAG and GFP. To investigate the function of the B peptide, we expressed these constructs in INS-1 832/3, a beta cell line derived from rat insulinomas. We performed glucose-stimulated insulin secretion assays using insulin ELISA, calcium imaging using a calcium dye, and immunofluorescence assays to determine B-peptide cellular localization.

<u>Results</u>: B-peptide is mainly localized to the endoplasmic reticulum in INS-1 832/3 cell. It also localized to the peroxisome and lysosome, but not the mitochondria. Moreover, overexpression of B-peptide increased basal phase insulin secretion compared to the FLAG-GFP control. This is associated with increased intracellular calcium compared to the FLAG-GFP control.

<u>Conclusions</u>: We conclude that the B-peptide positively regulates glucose-stimulated insulin secretion from beta cells, possibly by regulating calcium-mediated insulin secretion. Along with the fact that the B-peptide localizes to the endoplasmic reticulum, peroxisome, and lysosome, we suspect it might play a role in ER calcium handling within the beta cell. Future studies will look at protein binding partners of B-peptide and the function of the B-peptide in pancreatic islets isolated from diabetic mice.

## Surgical Management of Proximal Femur Metastatic Disease of Bone – A Pilot Study

## Arham Pasha, Jessica Goetz PhD, Palani Parmeswaran MS, Benjamin Miller MD

Introduction: The most common organ to be affected by metastatic cancer is the skeleton, and within the skeleton the axial skeleton[1]. The interaction of tumor cells and bone cells leads to metastatic bone disease and the disruption of bone metabolism[1]. The longer the course of cancer the higher likelihood exists of a sequential skeletal complication[1]. Metastasis to the bone causes significant morbidity including: pain, reduced mobility, hypercalcemia, pathological fractures, spinal cord or nerve root compression and bone marrow infiltration[1]. Metastatic damage to a bone reduces its load bearing capacity resulting in fractures, of which the most debilitating are long bone or epidural extension of the tumor[1]. Lastly, active orthopedic management early on can help reduce the probability of a pathological fracture forming, thus improving patient quality of life[1]. It is important that the surgical reconstruction be durable, with a minimal chance for failure or revision for the remainder of the patient's life.

**Purpose:** Our primary goal was to determine the relationship between defect size and load to failure, with and without intramedullary fixation, in the proximal femur. This is critical pilot data necessary to guide future studies investigating the role of fixation or replacement in metastatic disease of bone.

**Methods:** The research utilized Left-sided Sawbones bone models – synthetic femurs manufactured to reproduce the biomechanical properties of human bone. Three lesion sizes were created in the sawbones at the femoral calcar at increasing sizes relative to the lesser trochanter. Three large defects (5 cm in diameter), two total medium defects (4.5 cm in diameter), and two small defects (4 cm in diameter) were created. A control group was established for each defect group testing load to failure in the absence of fixation. The remaining sawbones in each group were stabilized with a Trigen InterTAN intramedullary nail. The load to failure was applied by an MTS machine with a 0.1 mm/s displacement to the femoral head until a fracture occurred.

Results: The moment arm for all tests was 65 mm and the angular displacement was 0.09 degrees/s. The small unnailed control (n=1) had a maximum force of 979 N, max displacement of 20.2 mm, Max Torque of 63.6 Nm, Radians of Rotation of 0.32, degrees of rotation of 18.4, Torsional stiffness 198 Nm/rad, and offset torsional stiffness of 48.5 (N/mm). The small nailed group (n=2) had a maximum average force of 1539.5 N, max average displacement of 19.75 mm, Max average Torque of 100.05 Nm, average Radians of Rotation of 0.315, average degrees of rotation of 17.97, average Torsional stiffness 320.5 Nm/rad, and average offset torsional stiffness of 78.25 (N/mm). The medium unnailed control group (n=1) had a maximum force of 838 N, max displacement of 24.4 mm, Max Torque of 54.5 Nm, Radians of Rotation of 0.39, degrees of rotation of 22.58, Torsional stiffness 138 Nm/rad, and offset torsional stiffness of 34.3 (N/mm). The medium nailed group (n=1) had a maximum force of 1355 N, max displacement of 21.97 mm, Max Torque of 88.1 Nm, Radians of Rotation of 0.35, degrees of rotation of 20.14, Torsional stiffness 251 Nm/rad, and offset torsional stiffness of 61.7 (N/mm). The Large unnailed control group(n=1) had a maximum force of 549 N, max displacement of 19.0 mm, Max Torque of 35.7 Nm, Radians of Rotation of 0.3, degrees of rotation of 17.24, Torsional stiffness 119 Nm/rad, and offset torsional stiffness of 28.9 (N/mm). The large nailed group (n=2) had a maximum average force of 936.5 N, max average displacement of 15.2 mm, Max average Torque of 60.9 Nm, average Radians of Rotation of 0.235, average degrees of rotation of 13.65, average Torsional stiffness 256 Nm/rad, and average offset torsional stiffness of 61.65 (N/mm).

**Conclusion/Discussion:** We found that intramedullary fixation provides increased strength to a defective femur, thus making it an important tool in the surgical management of proximal femur metastatic disease. As the defect size increases the difference between the force required to break stabilized and un-stabilized femurs become closer. However, it is still unclear on whether a critical size exists in that a nail will no longer suffice. More work is required to determine when prophylactic surgery is required, and whether optimal management consists of fixation or replacement.

1. Coleman, R.E., *Metastatic bone disease: clinical features, pathophysiology and treatment strategies.* Cancer Treat Rev, 2001. **27**(3): p. 165-76.

SRF Abstract 8/29/18

## Bone Regeneration and Fracture Healing Following Delivery of FGF-2, BMP-2, Insulin, and Vitamin D in a Type-2 Diabetic Rat Model

Madeline Peters, Douglas Fredericks, John Femino

**Introduction:** Diabetes Mellitus impairs the healing of fractures and there is a need for better therapeutics to stimulate bone regeneration in diabetic patients. It has been shown that local plasmid delivery of BMP-2 and FGF-2, impregnated in a collagen sponge, aids in the healing process of long bone fractures. Insulin and vitamin D have also been separately noted to stimulate bone regeneration and fracture healing. These effects have not been assessed when all of these factors are co-delivered in a diabetic animal model. We evaluated the effects on bone regeneration and fracture healing after delivery of the plasmids BMP-2 and FGF-2, along with insulin and vitamin D. Information gained from this study can provide new insights regarding the appropriate treatment methods for patients with fractures, specifically diabetic patients, as they are prone to adverse fracture healing.

**Purpose of the study:** We hypothesized that after creating a femoral defect, co-delivery of BMP-2 and FGF-2 plasmids, insulin, and vitamin D would augment bone regeneration in Type-2 diabetic and non-diabetic rats when compared with delivery of an empty collagen ceramic matrix. Determination of differences following each treatment method were determined quantitatively and qualitatively through X-ray comparisons, micro-CT analysis, and torsional testing.

**Methods:** A ZDF Rat model was used with 16 obese, type-2 diabetic rats and 16 lean, non-diabetic rats. Half of each group received either the empty collagen matrix (CCM) or the treatment with insulin, vitamin D, BMP-2 and FGF-2 plasmids embedded in a collagen matrix (CCM Combo). In both diabetic and non-diabetic rats, a 6-mm plate was placed in the mid-diaphyseal region of the femur and six screws were inserted to fix the plate to the bone. A Gigli wire was then used to create a 6 mm mid-diaphyseal femoral defect. Once the defect was removed, either the control collagen matrix or the collagen matrix containing the co-factors was placed within the defect. Plain radiographs, micro-CT, and torsional testing were utilized to evaluate the animals during the fourweek study.

**Results:** All implants were successfully placed in the left femur of both animal strains. Diabetic ZDF Obese rats implanted with the collagen ceramic matrix that contained the plasmids BMP-2 and FGF-2, insulin, and vitamin D had a high mortality rate due to improper absorption of vitamin D. No complications were noted in the ZDF-Lean rats with the impregnated matrices. Radiographic scoring of new bone formation (scale of 0-4) determined quality of healing in all rats. There were no statistical differences between the treated and control implants in the ZDF-Lean rats (CCM 0.25 and CCM Combo 0.43). CCM Combo implanted diabetic rats had significantly more bone formation within and around the defect compared to CCM implanted rats (CCM Combo 1.00 and CCM 0.17; p=0.004). MicroCT analysis of the implanted defects is pending due to maintenance on the SkyScan 1176. Therefore, torsional testing of the limbs has also been delayed. Limbs have been placed in -20 C freezer until testing can begin.

**Conclusion/Discussion:** Diabetic rats receiving implants with the plasmids BMP-2 and FGF-2, along with insulin and vitamin D, showed more bone regeneration than rats receiving an empty collagen matrix. Though the animals were assessed during the very early stages of defect healing, this demonstrates the beneficial effect that BMP-2, FGF-2, insulin, and vitamin D may have on bone regeneration. The autograft placed within the animals takes 16 weeks to heal, so further analysis of bone growth is needed between the two animal strains, as well as between the different treatment groups.

## Neurocognitive Function in Pediatric Brain Tumor Survivors

Jared Peterson, Amanda Grafft, Mariko Sato

**Background:** Brain tumor is the second most common malignancy, following leukemia, in children. Advances in clinical practice have improved outcomes, now reaching 75% survival. The increase in survival rates, however, has resulted in an increasing number of survivors with varying degrees of physical and cognitive impairment. Various studies showed survivors of pediatric brain tumor had deficits in verbal intelligence, non-verbal intelligence, attention, psychomotor skill, visual spatial skill, verbal memory, language, and academic achievement in reading, math, and spelling. It is important to understand the neurocognitive outcomes of children with brain tumor.

**Objectives:** To identify the patterns and risk factors of neurocognitive deficits by investigating neurocognitive testing results in pediatric brain tumor survivors at the University of Iowa.

**Methods:** Retrospective chart review of medical records was performed to identify pediatric brain tumor patients who had undergone neurocognitive testing. Both neurocognitive testing results and clinical records were reviewed. Patients with cognitive impairment prior to diagnosis were excluded. 10 testing domains were studied: verbal comprehension, perceptual reasoning, fluid reasoning, working memory, processing speed, reading, math, verbal learning, motor skills, and visual-motor integration. We also examined scores on the Behavior Rating Inventory of Executive Function (BRIEF) if available. Each test administered has a validated population mean and standard deviation to which we compared the scores of the identified patients. 95% confidence intervals were calculated to determine the statistical significance of our patients' scores from the population mean.

**Results:** We identified 69 patients (40 male) between the ages of 0.5 and 18.5 years at diagnosis (median 6.22 years). A total of 104 neurocognitive testing data were available for the study. The most common diagnoses in this cohort were Pilocytic Astrocytoma, Anaplastic Ependymoma, Medulloblastoma, and Low-Grade Glioma (11, 6, 6, and 6 patients respectively). 12 patients underwent neurocognitive testing prior to treatment and the results showed no statistical difference from population averages in any domains. Any treatment, such as surgery, chemotherapy, and/or radiation, affected patient's cognitive function in various domains. The surgery only group showed significant deficits in processing speed. The chemotherapy group showed deficits in motor skills and visual motor integration. The radiation group confirmed deficits in fluid reasoning, working memory, processing speed, math, and verbal learning as previously described. BRIEF data showed a significant portion of pediatric brain tumor patients have clinically significant executive function problems (7-19%, depending on the specific subcategory).

**Conclusion:** Neurocognitive deficits in pediatric brain tumor survivors were variable among tumor type and treatment. Surgery and radiation are the treatment modalities that cause the most deficits. However, these modalities of treatment are not avoidable due to lack of alternative therapies. By understanding baseline cognitive function prior to diagnosis, deficits after treatment and their trend, we may be able to develop appropriate interventions for patients in order for them to achieve a better quality of life.

# Improving Therapies for Metastatic Colorectal Cancer with Radiosensitizers and Stereotactic Body Radiotherapy

Vivian N. Pham; Steven N. Seyedin, MD, Bryan G. Allen, MD, PhD, Joseph Caster, MD, PhD

Introduction: Metastatic colorectal cancer (CRC) is a major challenge in clinical oncology. Chemotherapy can prolong survival, but resistance is inevitable and cancer-specific mortality remains very high. Checkpoint inhibitors (CPIs), such as inhibitory antibodies of the PD-L1 and CTLA-4 receptors have emerged as a promising new approach for chemotherapy-refractive solid tumor malignancies. Unfortunately, these treatments are not effective for the majority of patients with advanced CRC. Thus, there is a critical need to find novel ways to enhance the efficacy of the promising treatments for patients with metastatic CRC. Stereotactic body radiotherapy (SBRT) has shown potential to improve systemic immune responses to CPIs, though clinical responses have been modest and multiple mechanisms of resistance have been identified. Chief among these is increased activity of immunosuppressive cell populations, which can prevent the stimulation of an anti-cancer immune response and lead to inactivation of tumor-specific activated T-cells. A growing preclinical literature suggests that several classes of drugs, including inhibitors of HDAC, PARP, and PI3Ky can overcome resistance to CPIs by inhibiting the activity of immunosuppressive cell populations. Importantly, these drug classes are also potent radiosensitizers which enhance the effects of ionizing radiation. Our central hypothesis is that immune-modulating radiosensitizers may potently enhance systemic immune responses to SBRT and CPIs by simultaneously augmenting the stimulation of anti-tumor immunity and preventing downstream inhibition of activated tumor-specific T-cells. The overall goal of our research is to provide preclinical evidence to support our hypothesis and initiate clinical trials with clinically-utilized drugs. The goal of this summer research project was to confirm the in vitro efficacy of candidate drugs in syngeneic models of CRC.

**Hypothesis:** We hypothesize that the PARP inhibitor veliparib, the HDAC inhibitor entinostat, the ATR inhibitor VE 821, and the PI3Ky inhibitor IPI-549 will enhance the radiosensitivity of CT-26 and MC-38 murine syngeneic CRC cells.

**Methods:** Dose-responses to drug alone were assessed using clonogenic cell survival assays in order to determine IC90 of each inhibitor. Exponentially-growing MC38 and CT26 cells were plated and treated with drug at doses between 0-100 $\mu$ M. Drug-containing media was left on the cells for 24 hours or 7 days (veliparib) before replacing the media. Cells were placed in 4% oxygen incubator and were fixed and stained with Coomassie Blue after 7-10 days following treatment. Colonies were defined as collections of > 50 cells and manually counted. The surviving fraction was normalized to the plating efficiency in the absence of treatment.

To determine radiosensitivity of each inhibitor, MC38 and CT26 cells were plated and treated with IC90 concentration of drug alone for 1-48 hours and then treated with varying doses of ionizing radiation (from 0-8 Gy). Drug-containing media was replaced after 24-48 hours after radiation. Cells were incubated, fixed, and stained in an identical manner to that used for the dose-response assays.

**Results:** Dose-response colonogenic assays showed dose-dependent killing in both cell lines when treated with inhibitors alone. The IC90 was reached with concentrations of  $5\mu$ M veliparib,  $10\mu$ M IPI 549,  $0.5\mu$ M entinostat, and  $1\mu$ M VE 821.

Clonogenic cell survival assays showed enhanced killing in both cell lines when treated concurrently with XRT and Veliparib or VE-821 with sensitizer enhancement ratios between 1.7 and 2.1. In contrast to PARP and ATM inhibitors, HDAC inhibitors are epigenetic drugs which require some time to alter cellular function. Accordingly, we did not observe any significant enhancement of radiosensitivity with only 1-hour pretreatment with entinostat. However, 48 hours of pretreatment with 0.5-1  $\mu$ M entinostat dose-dependently enhanced the sensitivity of CT-26 cells to ionizing radiation. MC-38 cells were significantly more sensitive to entinostat and too few cells survived 48 hours of pre-treatment (even in the absence of radiation) for analysis. Reducing the pretreatment interval to 24 hours improved baseline survival (in the absence of radiation) and we observed significant radiosensitization. To our surprise, IPI-549 did not sensitize cells to ionizing radiation at any dose or pretreatment interval tested.

**Conclusions:** Our *in vitro* studies showed synergistic enhancement of tumor cell killing in both MC38 and CT26 cells lines by Veliparib, Entinostat, and VE-821 with radiation. Ongoing studies in our laboratory will investigate whether these drugs can enhance immune mediated tumor death in flow cytometry (i.e. MHC-1 expression, Calreticulin) and in syngeneic mouse models with anti-PD-1 therapy.

## Use of Cyproheptadine for the Treatment of Serotonin Syndrome: A case series and retrospective review

## Andrew Poggemiller, BSc<sup>1</sup>; Jared Frye, PharmD<sup>2</sup>; Colette Galet, PhD<sup>3</sup>; Patrick McGonagill, MD<sup>3</sup>; Kate O. Pape, PharmD<sup>2</sup>; Yuk M. Liu, MD<sup>3\*</sup>

<sup>1</sup>University of Iowa Carver College of Medicine, <sup>2</sup>Department of Pharmaceutical Care, <sup>3</sup>Department of Surgery, Division of Acute Care Surgery, University of Iowa Hospitals and Clinics, Iowa City, IA, United States

### Introduction/Hypothesis

In the last decade, the number of adult patients treated with antidepressants has increased in the United States. Paralleling this trend, the number of reported cases of serotonin syndrome (SS) has also increased. The most common treatment for SS is cessation of the causal agent and treatment with cyproheptadine. The recommended dosing of cyproheptadine is an initial dose of 12 mg then 2 mg every two hours until symptoms improve; however, literature describing the effectiveness of this regimen and the post-treatment outcomes is limited. Herein, we investigated the effectiveness of cyproheptadine for the treatment of SS through evaluation of patients' outcomes.

#### Methods

This is a non-interventional, retrospective chart review evaluating the outcomes of patients diagnosed with SS who were treated with cyproheptadine. Data including demographics, morbidity, mortality, overall length of stay (LOS), and LOS in each unit (intensive care unit (ICU) vs. floor unit) were collected. Descriptive statistics were obtained.

#### Results

Twenty eight patients were included in the study. A toxicologist formally diagnosed 17.9% of the admitted patients. The average LOS was  $11.2 \pm 16.8$  days. Twenty-two (78.6%) patients were treated in ICU and 6 (21.4%) patients were treated in the emergency department. The average duration of therapy was  $2.6 \pm 1.8$  days. The most common causative agents were an unknown agent, escitalopram, trazodone, paroxetine, citalopram, and lamotrigine, with some patients ingesting more than one drug. The average total dosage of cyproheptadine was  $47.6 \pm 32.0$  mg. The average time to first dose of cyproheptadine was  $1.1 \pm 2.0$  days from admission. Upon discontinuation of cyproheptadine, 96.4% of patients were alive on discharge; 3.6% did not survive.

## Conclusions

Most individuals who were diagnosed with SS and administered cyproheptadine had resolution of symptoms within 48 h, suggesting cyproheptadine as an effective treatment for SS. In addition, patients with SS that were treated with cyproheptadine had a low mortality rate compared to previous research. Further prospective studies are warranted to establish the optimal dosing regimen of cyproheptadine for the treatment of SS.

#### The Long-Term Outcome of Patients with Abnormal Head Position Due to Nystagmus treated with The Anderson-Kestenbaum Procedure

Hannah Pope, Aishwarya Kothapalli, Deborah Dawson PhD, Alina Dumitrescu MD

**Background:** Nystagmus, uncontrolled movements of the eyes, is a symptom of multiple ocular and non-ocular conditions. Nystagmus can occur due to lack of normal visual development, as well as due to neurological diseases or can be idiopathic. The nystagmus is characterized by waveform, amplitude, frequency and direction. A subset of patients with nystagmus develops a head position in which the nystagmus is weakest and thus allows for increased visual acuity and comfort, called the null zone. The head position is usually along the horizontal or vertical axis, however can also be a tilt, a combination of multiple axis or variable. If left untreated the anomalous head position (AHP) due to nystagmus can cause torticollis, as well as other muscular issues and potentially negative social consequences. As noted in previous studies the untreated head position can also lead to decreased reaction time and decreased visual acuity. In 1954, Anderson, Kestenbaum, and Goto each made significant contributions to a extraocular muscles (recess- resect) surgical procedure typically referred to as the Anderson-Kestenbaum procedure (AKP). The goal is to realign the null zone of the eyes thus resetting the AHP. Studies looking at short term follow-up have shown that the procedure is successful; however there have not been large studies looking at the success of the procedure in the long-term.

**Purpose:** The purpose of our study is to retrospectively analyze the long-term outcomes of the AKP. We are looking to determine if the procedure has lasting success. In addition, we hoped to identify variables that help determine patients that are the best candidate for the procedure, to adequately advise patients and families on if this procedure is the best option for them and to set their expectations for the future. We hypothesize that there are certain factors that can predict who is the best candidate for an optimal outcome of the AKP.

**Method:** A retrospective chart review of patients surgically treated with an AKP at UIHC from 1986-2017 for AHP due to nystagmus. Information gathered from the charts included the preoperative type of head position assumed by the patient and postoperative result, the age at the time of the first procedure, any underlying diagnosis if known, the type of nystagmus, preoperative notes, operative reports, the patient's vision before the procedure and at the last follow up, associated strabismus present before surgery or if any develops postoperatively. Success of the procedure was measured based on improvement in head position post- operatively, as well as if a head position recurred throughout the extended follow up time. An optimal outcome was determined to be an improvement in head position and no significant head position (less than 10 degrees) present at the last follow up appointment. A database was compiled using File Maker Pro and statistical analysis were performed using SPSS.

**Results:** 46 charts met the inclusion criteria. Our analysis showed that 91.3% of the patients in the study exhibited an improved head position at the last follow-up appointment, and 56.5% were overall determined to have an optimal outcome. However, 73.9% of patients had a residual head position at their last follow up appointment, and of those patients, 58.8% of the head positions were significant (greater than 10 degrees). Of the 34 patients who had a recurrence of a head position, 38.2% had the same head position, and 61.8% developed a different head position. A trend of decreased frequency of improvement in AHP and optimal outcome for those who had the procedure after the age of 145 months was noted. There also was a decrease in rates of optimal outcome as the length of follow up time increased. Of the 20 patients who did not have strabismus prior to the surgery, 40% of them developed strabismus after the procedure. Patients with head positions, 50%, then followed by vertical axis, 33%. Suboptimal outcomes were due to residual AHP or acquisition of a new head position. Of the 46 patients 33% showed an improvement in vision from the pre-op appointment to their last follow up. the other patients either did not improve (15%), did not show any change (37%) or did not have visual acuity measured at both appointments (15%).

**Conclusion:** Overall the number of patients treated with this procedure is small. Setting realistic expectations for the patient preoperatively is the most important recommendation from this study. While improvement of head position is likely, it is also likely that a certain degree of head position will still be left after the procedure, and the same head position or a new head position could develop as time progresses. Age group and axis of head turn should all be taken under consideration when informing the patients about this procedure and the likelihood of an optimal outcome. However, no single identified variable guarantees success. Alternative treatments may prove useful to address the underlying issue of Nystagmus. Future studies could look at the impact of medically treating nystagmus and the outcome it could have on head position to either be used in conjunction with or in opposition to the procedure. While this procedure has proved to be helpful for many, it is not a cure-all and patients should be advised accordingly.

## Comparison of Outcomes in Extremely Premature Babies with Respiratory Distress Syndrome through Administration of Curosurf and Survanta Greg Power, Nichole Nidey, Sarah Tierney, Kelli Ryckman, John Dagle

**Background/Introduction:** Lung development begins early in a pregnancy and continues until after birth; it is therefore a common problem that premature babies suffer from a lack of surfactant production and neonatal respiratory distress syndrome. Artificial surfactants are available that can be given to these patients. Research in the past has shown that for patients born 24 to 29 weeks of gestation, Curosurf may offer benefits over Survanta. However, for extremely premature infants, it is unknown whether one surfactant is more efficacious.

**Purpose of study:** In the University of Iowa NICU, three different surfactants (Infasurf, Curosurf and Survanta) are currently being administered to premature babies with neonatal respiratory distress (RDS). The most common treatment for extremely premature babies is Survanta, however, this study seeks to see whether Curosurf may be a superior treatment for extremely preterm infants with respiratory distress syndrome than Survanta.

**Method:** This was retrospective chart review study. We examined the patients born at the University of Iowa with a birth weight under 750 grams who received a surfactant dose during the period of January 2015 until March 2018 – a population of 94 patients. We looked at the primary outcomes of average time between first and second dose, the number of doses given, and patient mortality. Secondary outcomes included air leak disorders, and pulmonary hypertension. We divided the patients based on whether the first surfactant given was Survanta or Curosurf, and then stratified the patients by birth weight: 600 grams and under (45 patients) and 601 grams to 750 grams (49 patients). We compared the groups via Fisher's Exact Test and Chi Square analyses to see if the differences between the groups were significant.

**Results:** When comparing all patients born under 750 grams, patients who first received Curosurf compared to Survanta received significantly fewer doses (2.67 vs. 4.06, p=.0032), and had significantly reduced mortality (0 vs. 27.94%, p=.0024). Patients receiving Curosurf first also saw a non-significant increase in time between first and second dose (88.11 vs. 53.86 hours, p=.1397), as well as non-significant decreases in the secondary outcomes of PIE, pneumothorax, and pulmonary HTN. In our stratified comparison of patients born 600 grams or under, the sample size for Curosurf (n=3) was too small to find significant differences in any outcome. The comparison of patients born 601 to 750 grams showed patients who first received Survanta had a significant reduction in mortality (0 vs. 29.63%, p=.0064), and non-significant improvements in the other outcomes.

**Conclusion/Discussion:** Our initial retrospective study shows that Curosurf may be a superior treatment for extremely premature infants than Survanta. We found a significant decrease in mortality for all patients under 750 grams, as well as those between 601 and 750 grams. Although the limited sample size for patients under 600 grams made it impossible to find significant differences, the patients that did receive Curosurf showed good results. The significant improvements that were found suggest that further research, including a randomized control trial, will show Curosurf to be a viable, and perhaps better, alternative to Survanta for extremely premature infants with RDS.

## Upstream Obstetrics: Assessing the Prevalence of Food Insecurity in a High-risk Obstetrics Population

Deepika Raghavan, BS; Michael Haugsdal, MD; Craig Syrop, MD, MHCDS

### Background:

Food security is a social determinant of health defined as the availability of and access to adequate food. Barriers contributing to food insecurity include physical, social, and economic factors such as time, money, and transportation. While food insecurity affects all age groups and ethnicities, the prevalence of food insecurity is notably higher in women when compared to men. Co-morbid medical conditions such as obesity, hypertension, and diabetes can be exacerbated during pregnancy. Furthermore, food insecurity may heighten risks for poor maternal health, perinatal complications, and poor pregnancy outcomes particularly if compounded by existing co-morbidities in high-risk pregnancies.

### Purpose:

The Upstream Clinic is a quality improvement project initiated by students and faculty in the Department of Obstetrics and Gynecology that seeks to address food insecurity in high-risk obstetrics patients. This study aims to identify the prevalence and impact of food insecurity among pregnant patients in the clinic population. Information collected through this study will be used to assess the effect of social needs on pregnancy outcomes.

### Methods:

Validated survey questions from Health Leads regarding food insecurity were administered to patients attending the High-risk Obstetrics (HROB) Clinic at the University of Iowa Hospitals and Clinics (UIHC). Data including demographics, survey response(s), and predominant co-morbidities affecting the pregnancy were recorded. Clinic personnel reviewed the surveys in real-time. A "yes" response to any of the "food need" questions was designated as "screen positive." Screen positive individuals were offered counseling by an Upstream Clinic team member as a means to identify nutrition resources in the patient's residential area. Data collected from the Upstream Clinic survey were used to assess 1) prevalence of social needs in the UIHC HROB population, 2) correlation of social needs with common medical co-morbidities, 3) possible effects of social needs on pregnancy outcomes by comparing survey data with variables from an existing UIHC HROB database.

#### **Results:**

One hundred eighty-five women attending the HROB clinic completed the Upstream Clinic survey. Twenty-four percent (44/185) were screen positive while 76% (141/185) were screen negative. Diabetes was the most prevalent comorbidity for screen positive patients (25/44, 57%). Amongst all screened patients, other common co-morbidities included obesity (33/185, 18%) and hypertension (38/185, 21%). More than one co-morbidity was self-reported by 32% (59/185) of respondents.

In the first seven-month period of this Upstream Clinic (1/1/18-7/31/18), 38% (71/185) have delivered and 20% (14/71) of delivered patients were screen positive. Patients with perinatal diabetes accounted for 56% (40/71) delivered patients. Within this subgroup, 22% (9/40) were screen positive and 78% (31/40) were screen negative. Poor control of diabetes was defined as an abnormal hemoglobin A1C (HgbA1C) > 6.5%. The prevalence of abnormal HgbA1C (at HROB enrollment) was 66% (6/9) for screen positive individuals with diabetes versus 39% (12/31) for screen negative individuals. There was no difference in gestational age at delivery or prevalence of large for gestational age (LGA) neonates in either group.

#### Conclusion:

While 12% of adults in Iowa are food insecure, food insecurity appears to be highly prevalent amongst high-risk obstetric patients (24%), and particularly amongst perinatal diabetes patients (22%). Although statistically significant differences were not found due to limited sample size in the early stages of this initiative, this study suggests that food insecurity may be associated with adverse health outcomes such as poor maternal control of diabetes. As the population sample size of women served by the Upstream Clinic intervention increases, the impact of food insecurity on obstetric and neonatal outcomes will continue to be assessed.

## Quality of Life Among Pediatric Patients with Limb Girdle Muscular Dystrophy type 2I

M. E. Rasor, BS,<sup>1</sup> C. M. Stephan, MA, BSN<sup>1</sup> C. L. Miller, BS, BSN,<sup>1</sup> M. B. Zimmerman, PhD,<sup>3</sup> K. D. Mathews, MD<sup>1,4</sup>

<sup>1</sup>Department of Pediatrics, University of Iowa Carver College of Medicine, Iowa City, IA <sup>2</sup>Center for Disabilities and Development, University of Iowa Children's Hospital, Iowa City, IA <sup>3</sup>Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, IA <sup>4</sup>Department of Neurology, University of Iowa Carver College of Medicine, Iowa City, IA

**Introduction.** Dystroglycanopathies are a group of autosomal recessive disorders resulting from the hypoglycosylation of  $\alpha$ -dystroglycan. Disruption of this component of the dystrophin glycoprotein complex results in a decrease in membrane stability of myocytes. Mutations in any of the 18 known genes required for a normal alpha-dystroglycan glycosylation can result in muscular dystrophy, with or without multisystem involvement.<sup>1</sup> FKRP mutations are the most common cause of a dystroglycanopathy and typically cause limb girdle muscular dystrophy, type 2I (LGMD2I).<sup>1</sup> Quality of life surveys are multidimensional assessments of the physical, psychological, and social functioning of an individual, which may be impacted by one's health and are an important outcome measure in therapeutical trials.<sup>2</sup> There is currently no data on quality of life for children with dystroglycanopathies. Here we describe QOL assessment of children with LGMD2I and compare our findings to other pediatric neuromuscular conditions. These results provide a baseline against which to measure the impact of future therapies on patient's quality of life.

**Objective.** To evaluate quality of life data reported by a cohort of children with *FKRP* mutations and their parents relative to disease stage.

**Methods.** Children enrolled in a dystroglycanopathy natural history study were invited to complete the PedsQL<sup>TM</sup>, the PROMIS<sup>®</sup> Pediatric Pain Interference and Pediatric Fatigue short forms, and functional motor testing at annual visits. The mean PedsQL<sup>TM</sup> score for each domain and a total score was obtained by fitting a generalized linear model using the GEE (generalized estimating equations) method. We used linear regression to correlate PedsQL<sup>TM</sup> scores to participant performance on two physical therapy measures including time supine to standing and time to climb 4 stairs. Correlation coefficients were calculated using the linear mixed effects (LME) model.

**Results.** There was no relationship between  $\text{PedsQL}^{\text{TM}}$  scores and age in any domain, but all domains showed a significant correlation with motor function. This relationship was strongest for the physical function domain (r=0.67) and weakest for the emotional function domain (r = 0.28). There is a significant correlation between all child-reported  $\text{PedsQL}^{\text{TM}}$  domain scores and both the PROMIS<sup>®</sup> Pediatric Pain and Fatigue Interference scores. The correlation was highest for the physical function domain and lowest for emotional function domain for both pain and fatigue. **Conclusions.** We found that a decline in motor function is associated with a lower  $\text{PedsQL}^{\text{TM}}$  score. The effect of this decline in motor function on quality of life varies by domain with least impact on emotional functioning. Quality of life scores for children with Limb Girdle Muscular Dystrophy Type 2I (LGMD2I) are similar to those reported for other childhood neuromuscular diseases. Both children and their parents report a decline in quality of life with increasing pain and fatigue.

## Neuropsychological Profiles of Young Participants in Flag vs. Tackle Football

Jasmine Roghair, Patricia Espe-Pfeifer, Ph.D., Andrew Peterson, MD, MSPH

**Background:** 2.8 million children between grades 2-7 participate in youth football each year. Previous studies have found that reported injury rates are slightly higher in flag (non-contact) football than in tackle. However, intrinsic differences may exist between children and families that choose to play flag versus tackle football.

**<u>Hypothesis</u>**: Children who play flag football will score differently than children who play tackle football on validated neuropsychological tests.

**Methods:** The following validated neuropsychological tests/questionnaires were administered to the athlete:

- Wechsler Abbreviated Scale of Intelligence-Second Edition, providing a 2 subtest IQ estimate (FSIQ-2)
- 2. Trail Making Test, Children's version, Parts A & B, measuring mental set-shifting, attention, and cognitive processing speed
- 3. WISC-IV Integrated Digit Span and Spatial Span Subtests, measuring working memory and spatial processing

4. Beck Self-Concept Inventory for Youth (BSCI-Y), measuring the child's perception of self-concept The following questionnaire was administered to the parent/guardian of the athlete:

- 1. Achenbach Child Behavior Checklist-Parent Report Form, measuring internalizing and externalizing behaviors and symptoms
- 2. Behavior Rating Inventory of Executive Function-Parent Form, measuring aspects of executive functioning and yielding a behavioral regulation index, metacognition index, and global executive composite

3. Standard survey determining the reasons for enrollment in each type and concussion risk perceptions Means for FSIQ-2, Trails A, Trails B, Digit Span, Spatial Span Forward, and Spatial Span Backward were calculated and compared.

**<u>Results</u>:** Enrollment ongoing. So far, nine tackle and two flag football players (grades 4-6) were enrolled from a youth football league. Most parents indicated on the standard survey that they chose to put their child in tackle instead of flag football to prepare them for junior high football. On a scale of one (very safe) to ten (very risky) flag football parents on average rated concussion risk in youth football a 6.5 (n=2) versus parents of tackle football a 4.3 (n=8).

	FSIQ-2	Trails A	Trails B	Digit Snan	Spatial Span Forward	Spatial Span Backward
Taalda	100	Dary 12 70	Darry 27.96	11	115	10.5
I ackie	100	<b>Kaw:</b> 15.79	<b>Kaw:</b> 57.80	11	11.3	10.5
Football		seconds	seconds			
(n=9)		Scaled: 0.08	Scaled: -0.64			
Flag	108	Raw: 16.76	Raw: 29.04	9	10.5	11.2
Football		seconds	seconds			
(n=2)		Scaled: 0.44	Scaled: 0.38			

Table 1.Ongoing means calculated from scaled scores (unless otherwise indicated) for tackle vs. flag football.

**Discussion**: As enrollment continues, we aim to determine if children who choose to play tackle football score differently on standardized neuropsychological testing than children who choose to play flag football.

Guillermo Romano Ibarra, M3G Stoltz Lab, Summer 2018 Medical Student Research Conference: Sept 12-13

## CF airway smooth muscle transcriptome guides identification of small molecule agents with therapeutic potential for asthma.

Abnormal airway smooth muscle (ASM) function is a feature of both asthma and cystic fibrosis (CF), resulting in airflow obstruction, a major morbidity in both diseases. Previously, it was unknown whether this feature in CF resulted from direct loss of CF transmembrane conductance regulator (CFTR) function or was secondary to chronic infection and inflammation. Recent work done by our group identified CFTR expression in ASM sarcoplasmic reticulum. Loss of CFTR led to abnormal calcium handling and increased ASM tone in newborn pigs. Further work using the transcriptome of CF newborn pig ASM identified PYK2 as a novel molecular target and a small molecule PYK2 inhibitor (NVP-TAE684) was found to reduce ASM contraction and reduce methacholine-induced bronchoconstriction in CF *in-vitro* and *in-vivo* models.

In this work, we use a similar approach and use connectivity mapping to identify small molecules that elicit transcriptome "signatures" opposite to those found in CF newborn pig ASM. We hypothesized that molecules with these transcriptome signatures should reduce methacholine-induced airway constriction in newborn pig airways by inducing transcriptional changes. Using precision-cut lung slices obtained from newborn pigs, we tested the ability of various compounds to alter ASM responsiveness to methacholine. We investigated Artesunate, BRD1812, CGK, and FCCP which are clinically relevant molecules with previously unidentified biological activity in ASM. None of the four compounds affected airway narrowing following methacholine treatment. However, we did find that these molecules changed the kinetics of airway contraction. Further insight into how these molecules influence signaling pathways and alter gene expression in CF and asthma could help guide therapeutic development that reduce airflow obstruction in both diseases.

**Title:** Cellphone administration of the Short Hip Osteoarthritis Outcome Score (HOOS- PS) and Pain Subscale (HOOS-PAIN) using Text Messaging

Name: Patrick Rooney Mentor: Robert Westermann, MD Collaborators: Elizabeth Scott, MD; Chris A Anthony, MD; T S Lynch, MD; Michael Willey, MD

PURPOSE: The purpose of the present study was to evaluate the efficacy of administration of hip specific outcome instruments over a mobile phone based text messaging platform delivered outside of a clinical encounter.

METHODS: Consecutive patients (n=72) presenting to a Hip Preservation Clinic for evaluation of hip pain were enrolled. Subjects completed the Hip disability and Osteoarthritis Outcome Score Short Form physical function and Pain subscales (HOOS-PS, HOOS-PAIN) via a handheld tablet. The subsequent day, patients were asked to complete the same PRO instruments via a custom-built text messaging software program. Automated reminders were sent to patients to encourage completion of unanswered questions. Correlation between in-office and mobile phone delivery of the PROs were assessed. We defined excellent reproducibility to be an intraclass correlation coefficient (ICC) of >0.75. Demographic data including age, gender, and diagnosis were retrospectively collected.

RESULTS: There was a 94% (64/69) completion rate for patients who received the outcome instrument questionnaire over text messaging. The mean age was  $31\pm10.5$  years (range 15-55) and 70% of respondents were female. The ICC between in-office electronic and at-home mobile phone delivery of HOOS-PS was 0.72 (95% confidence interval [CI] 0.58-0.81) and HOOS-Pain was 0.80 (95% CI 0.69-0.87). Cell phone scores were lower than in-office scores by an average  $8.7\pm12.6$  and  $7.5\pm12.1$  points for HOOS-PS and HOOS-Pain, respectively. Patients most frequently requested morning communication between 8AM-Noon (65%) to afternoon communication 4-8PM (35%).

CONCLUSION: HOOS-PS and HOOS-Pain PRO instruments administered via mobile phone text messaging demonstrates good to excellent reproducibility and an equal completion rate compared to traditional in office methods. Mobile phone delivery utilizing our software algorithms may be a valid method for administration of other PROs in this population and both eliminates in-office testing, allowing communication with patients anytime and anywhere.

#### Post-operative Pain Management of Pediatric Urological Procedures

Zachary Rye M1 Dr. Storm, Pediatric Urology

A major problem impacting the American public is the over prescription of opioids, which adds to the opioid epidemic in the USA. There have been numerous studies conducted showing that sales of prescription opioids in the United States have quadrupled, but the overall amount of pain that Americans are reporting isn't changing. One of the major reasons that opioids are being over prescribed by physicians is because physicians are uncertain on the amount of opioids needed by each individual patient post-operation. Physicians prescribing and exposing adult patients to narcotics to date, has been well documented, however, prescribing and exposing pediatric patients to narcotics has been much less documented. Our aim in this study was to document the levels of pain reported by the post-operative pediatric patients as well as the amount of narcotics used to understand the dosage needed for patients based on factors such as: age, sex, procedure performed, past exposure to narcotics, etc.

This prospective study was conducted by consenting patients the day of surgery, as well as having them fill out a pre-operative questionnaire ranking their pre-operative pain levels as well as any previous usage of narcotic pain medicine. Post-operatively, the patients (or parents) would receive a text message every evening at 8pm, starting the day after surgery, for the next 7 days. The text message asked for, over the previous 24 hours, the patients pain on a scale of 0-10 as well as the doses of oxycodone, acetaminophen, and ibuprofen that the child needed. The data was collected and analyzed for the amount of pain reported by the patients as well as the dosage that was need for each individual patient to evaluate for: over-prescription, under-prescription, or adequate prescription dosage.

The number of participants that had completed this study were 16, with all 16 being male. The average age of the participants was 5 years, with the youngest patient being 8 months old and the oldest patient being 15 years old. The level of pain started out on average at 5.1/10 for day 1, 3.5/10 for day 2, 2.5/10 for day 3, 1.6/10 for day 4, 1.3/10 for day 5, 0.8/10 for day 6, and 0.7/10 for day 7. Oxycodone started out with an average dosage taken on day 1 of 1.6, then trended down with 1.0 doses on day 2, and then from day 3 through day 7 the doses taken were 0.2, 0.1, 0.3, 0.1, and 0.1 respectively. The acetaminophen and ibuprofen doses per day followed the same trend down with the acetaminophen dosage from day 1 through day 7 being 2.5, 1.5, 1.4, 0.8, 0.3, 0.2, and 0.3 respectively. The Ibuprofen dosage from day 1 through day 7 was 2.9, 2.5, 1.8, 1.3, 0.6, 0.8, and 0.2 doses per day respectively. The average number of doses needed by the patients was 2.6 doses of oxycodone, 6.5 doses of acetaminophen, and 9.5 doses of ibuprofen. The average number of doses given to the patients were 13.3 doses of oxycodone, 27.3 doses of acetaminophen, and 41.5 doses of ibuprofen. The percentage of medication that was used compared to dosage prescribed post-operatively was 19.5% usage of oxycodone, 23.8% usage of acetaminophen, and 22.9% usage of ibuprofen. The average number of days that the participants were on the medications before they stopped using them was 1.8 days for oxycodone, 3.9 days for acetaminophen, and 4.4 days for ibuprofen.

In conclusion, the data shows that post-operative medications are overprescribed. The average patient in this study received roughly 5 times the amount of oxycodone, acetaminophen, and ibuprofen that they needed and for all 3 drugs, the patients on average took no more medication after 5 days. The levels of pain associated with the surgeries also remained low and constant after 3 days.

Title: Structure of a Mutant Form of PCNA Deficient in Error-Free Repair Presenter: Miranda Schene Mentor: Todd Washington

#### Background

DNA damage is a major problem for cells during replication, when this damage can cause the replication fork to stall and potentially lead to cell death. In order to continue replication, the cell can utilize a few different methods. One of these methods is translesion synthesis, where a specialized repair polymerase simply replicates over the



Figure 1: Illustration of DNA Repair Pathways

damage. This method overcomes fork stall, but can lead to mutations because these repair polymerases are very errorprone. Another method that the cell can use is template switching. In this process, the replication fork "retreats" slightly, forming a structure that allows DNA replication to continue, using the undamaged strand as a template for replication of the damaged strand. Replication then continues with the DNA damage bypassed, and because an undamaged strand was used as a template, this pathway is relatively error-free. These damage repair pathways are regulated by a protein called PCNA, which is a trimeric sliding clamp that serves as a "toolbelt" for other DNA repair enzymes. Another group has found that the K168A mutation in PCNA is deficient in the error-free repair pathway, but the reason for this deficiency is unknown.

#### Purpose

In this study, we examined the structure of the K168A mutant form of PCNA, a protein that is an important component in the initiation and regulation of DNA damage repair, in order to determine whether there were any structural explanations for its observed deficiency in error-free repair.

#### Method

Q5 mutagenesis was performed on wild-type yeast PCNA. This mutant yPCNA gene was transformed into BL21 E. Coli cells for protein expression. After expression, the protein was purified over nickel affinity and S200 size exclusion columns. Once purified, hanging drop crystallography trays were set up, and once crystals formed, x-ray crystallography was performed to elucidate the protein structure.

#### Results

S200 size exclusion chromatography showed that there was an unusually high appearance of dimers and monomers in the PCNA K168A purification, whereas in the wild-type PCNA, the trimer is very stable and does not easily dissociate. Upon solving the structure and comparing it to a previously-solved structure of wild-type PCNA, there were no significant global structural changes caused by the K168A mutation. However, when the monomer interactions were examined, the distance between monomers in the K168A trimer was significantly larger than the distance between wild-type monomers. This reinforces the trimer instability observed in the S200 column.



Figure 2: Structure of PCNA K168A (yellow) aligned with a structure of wild-type PCNA (blue)

#### Conclusion

The K168A PCNA mutation, which is deficient in error-free damage repair, has a deficiency in trimer stability due to a slight structural change caused by the mutation. Further work needs to be done to determine whether and how this instability contributes to the observed deficiency.

## Assessing Reliability and Validity of Measuring Body Composition with A-mode Ultrasound

Name: Luke Schiller Faculty Mentor: Michael Willey, MD

## Objective

Sarcopenia, a condition characterized by decreased skeletal muscle mass and function, is associated with increased morbidity and mortality following fracture of the hip or acetabulum. The gold standard for assessment of sarcopenia is computed tomography (CT) or magnetic resonance imaging (MRI). Air displacement plethysmography (ADP) is another validated tool for measuring body composition. These modalities require large and expensive equipment, are associated with high costs, and CT exposes patients to ionizing radiation. Ultrasound is a portable and low-cost modality for identifying sarcopenia without radiation exposure, and may offer an alternative screening method. The purpose of this study was to assess reliability and validity of amplitude-mode ultrasound estimates to screen patients for sarcopenia.

## Methods

31 subjects were recruited and underwent serial body composition assessments using ultrasound and ADP. Two independent raters performed two serial ultrasound measures, separated by >24 hours, at three sites as described by Pollack. Intrarater and interrater reliability was assessed using intraclass correlation coefficient (ICC) and Bland-Altmann analysis. Validity of ultrasound measures was assessed by comparison with ADP and CT scans using the same analyses.

## Results

Intrarater and interrater reliability was excellent, with ICC values (%BF, Fat Mass, Fat Free Mass) of 0.87, 0.90, and 0.99 (rater 1); 0.80, 0.90, and 0.98 (rater 2); and 0.87, 0.91, 0.98. Fat free mass measured by ultrasound was strongly correlated with ADP measures (ICC=0.96). Bland-Altman analysis demonstrated no systematic bias in ultrasound measures between raters, or when compared with ADP fat free mass. Fat free mass showed moderate correlation with psoas index measured by CT scan (r=0.6770, p<0.0001), which is similar to other literature on the subject.

## Conclusions

Amplitude-mode ultrasound is a low-cost alternative to CT, MRI, or ADP that provides reliable and accurate estimates of fat free mass. Ultrasound is a viable alternative for sarcopenia screening and preoperative risk stratification.

#### Student: Eric Schnieders

#### Mentor: Dr. Resmiye Oral

**Title:** Impact of Trauma Informed Assessment on case identification at the Child Assessment Clinic that requires referral for services

#### Abstract:

Two-generational trauma-informed assessment (TIA) helps providers conduct holistic family-centered family well-being assessment (FWbA) by including family members' trauma history, resilience, and needs assessment in the diagnostic process. Our study compares two groups of families seen in a child abuse clinic (CAC) before and after FWbA was implemented in 2014. This subsection of the larger study conducted retrospective chart review of 364 children, divided into two groups to compare them in regard to service referral rates for children and their caretakers.: Group 1 subjects (n=176, 2014-2016) received FWbA (study group). Group 2 subjects (n=188, 2011-2013) received brief psychosocial evaluation without FWbA. Overall, the number of services children and caretakers were referred to was significantly higher in Group 1;  $2.7 \pm 1.5$  vs  $1.5 \pm 1.3$ , p<0.0001 for children and  $3.0 \pm 1.9$  vs.  $1.2 \pm 1.2$ , p<0.0001 for adults. Children in Group 1 were referred to select services at higher rates, which included behavioral health intervention services, Big Brothers Big Sisters, parent-child interaction therapy, Pediatric-Integrated Health Services (for all, p<0.0001). Caretakers in Group 1 were referred to Adult Integrated Health Services (p=0.0257), food assistance/food stamps (p=0.0058), childcare assistance (p=0.0120), unemployment/job training assistance (p=0.0122), family therapy (p<0.0001), batterer's education (p=0.0071), outpatient psychotherapy (p<0.0001), psychiatry (p<0.0001), substance abuse services (p=0.0041), parenting education (p=0.0018) at statistically significantly higher rates. Conclusion: Since two-generational FWbA helps uncover more trauma history in both caretakers and children, it allows providers to refer patients to more services than conventional brief psychosocial assessment alone.

## The Impact of Adverse Childhood Experiences (ACEs) on Burn Outcomes in Pediatric Patients

Laura Scieszinski, BA<sup>1</sup>, Colette Galet, PhD<sup>2</sup>, Lucy Wibbenmeyer, MD<sup>2</sup>, FACS

<sup>1</sup>University of Iowa, Carver College of Medicine, <sup>2</sup>Department of Surgery, University of Iowa Hospitals and Clinics

**Introduction:** Adverse childhood experiences (ACEs) are defined as childhood trauma that occurs before the age of 18 [1,2]. ACEs include physical abuse, emotional abuse, sexual abuse, domestic violence, parental divorce, and family member substance use, withdrawal/suicidal ideation, imprisonment of someone close, prejudice, separation from parent, and experiencing theft or abduction [2]. Childhood trauma can lead to toxic stress and development of negative health behaviors and chronic diseases [2]. Current ACE research primarily focuses on adult ACEs. Adults with high-ACEs ( $\geq$ 4) are significantly more prone to ischemic heart disease, chronic lung disease, diabetes, liver disease, and mental health diseases [2]. A recent study from our team showed that adult patients treated for burns had 1.2 times more ACEs than the greater Iowa population [3]. Moreover, those burn patients with high-ACEs also reported higher daily worst pain and less control over pain [4]. Yet, the interaction between parent ACEs and their children's subsequent health is poorly studied. Reports showed that, in the general population, parental ACEs positively correlated with child risk of suspected developmental delays [4]. Children at high-risk of maltreatment with  $\geq$  3 ACEs were more likely to experience an illness requiring a doctor and children with  $\geq$ 5 ACEs were more likely to have poor health [5]. Herein, we aimed at assessing both parent and children ACE levels on presentation to the University of Iowa Hospitals and Clinics (UIHC) burn unit.

**Purpose:** We hypothesize that the parents of children with burn injuries will have been exposed to high-ACEs and the children themselves will have been exposed to  $\geq 1$  ACE.

**Methods:** This is an ongoing, prospective study that uses a within patient-design study. Adult and <18 subjects are approached for study entry. For children, upon consent, parents complete a self-report ACE-18 survey. ACE-18 questions included parent ACEs and child participant ACEs. Parents also complete a strengths and needs survey (Individual and Family Strengths and Needs Assessment; Safe Environment for Every Kid), and parent resiliency questionnaire (Brief Resiliency Scale). Charts are reviewed for demographics, burn injury data, and hospital course. For this interim analysis, baseline analysis was completed with chi-square and t-tests when appropriate. Analysis was performed either by comparing ages (<5 years old and  $\geq$ 5 years old) or the number of child ACEs (0 ACEs and  $\geq$ 1 ACE). Significance was assumed at p <0.05. The hospital's Institutional Review Board approved the study.

**Results:** Sixty-nine pediatric participants were included in the analysis. The average age was  $5.3 \pm 5.0$  years (63.8% < 5 years of age). The majority was male (57% male) and white (68% white). Thirty percent were admitted. The average total burn surface area (TBSA) was 4.13%. Parents reported  $2.4 \pm 2.9$  ACEs for themselves and  $1.3 \pm 1.8$  ACEs for their children. Parents of children with  $\geq 1$  ACE had higher ACEs themselves ( $6.1 \pm 5.2$  parent ACEs with children  $\geq 1$  ACE compared to  $3.9 \pm 4.2$  parent ACEs with children 0 ACEs; p < 0.001). Families of children with 0 ACEs were more likely to own their home (p < 0.03). The average family needs were  $2 \pm 2.2$ ; 46.4% reported 2 or more needs. Comparing the population by age, children  $\geq 5$  years old were more likely to have parents with more ACEs ( $3.9 \pm 3.9$  vs.  $1.5 \pm 1.6$ ; p < 0.001) and to have more ACEs themselves ( $2.1 \pm 2.6$  vs.  $0.8 \pm 0.9$ ; p < 0.001). Families of children  $\geq 5$  years were more likely to have more than 2 needs (p < 0.027).

**Conclusions/Discussion:** Trauma Informed Care (TIC), including ACE screening, seeks to understand the individual patient and their family system. This understanding enables the health care provider to engage their strengths and take into consideration their needs when devising a care plan. TIC may help identify those in need of assistance to facilitate a successful recovery. Our data suggest that families of burned children and children themselves, especially those >5 years, have an ACE burden as well as a significant number of needs that require a sensitive and well informed approach.

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#### Morbid Obesity: Effects on Cervical Cancer Screening and Presentation

Kelsey Sheets, BA, Haley Hansen, BS, Colette Gnade, MD, Abbey Hardy-Fairbanks, MD, Colleen Stockdale, MS, MD, Department of OB/GYN, UIHC

**Background**: The prevalence of obesity is steadily rising in the United States. According to the CDC, 39.8% of adult Americans are classified as obese. The growing obese patient population continues to have a greater risk for the development of certain cancers and faces poorer treatment outcomes than normal weight patients. Morbid obesity, specifically, is suggested to be an independent risk factor for death from cervical cancer.

**Aims/Hypothesis**: This study aims to assess the impact of obesity on cervical cancer presentation, stage at diagnosis, and screening rates in comparison with previous studies on the topic. We predict that morbidly obese women (BMI > 40) are more likely to present with symptoms of cervical cancer rather than through preventative screening (pap smear). We also predict that morbidly obese women are less likely to have correct cervical cancer screening compared to non-obese patients and are more likely to be diagnosed at a more advanced stage of cervical cancer.

**Methods**: This retrospective cohort study consisted of cervical cancer patients treated at the University of Iowa Hospitals and Clinics from 1986 through 2018. This preliminary data consists of 668 total patients with 262 classified as obese (BMI > 30) and 387 classified as non-obese. The patients were categorized as non-obese (BMI < 30), obese (BMI 30-39.9) in 196 of 262, and morbidly obese (BMI > 40) in 66 of 262. Other factors affecting cervical cancer were included in the data analysis: age, race, smoking status, nodal metastasis, and the use of chemotherapy and radiation therapy with surgical treatment.

**Results**: Many women with cervical cancer diagnosis did not receive recommended cervical cancer screening. 34.3% of obese women had correct screenings vs. 42.6% of non-obese women, p-value 0.03. Amongst all obese patients, 28.8% of morbidly obese women had correct screening vs. 47.2% of obese women, p-value 0.02. Correspondingly, symptoms and stage of diagnosis were more advanced. 74.2% of morbidly obese patients presented with symptoms of cervical cancer instead of through screening tests compared to 59.8% of obese patients (p-value 0.03). 12.5% of obese women presented at an advanced diagnosis, compared with 14.6% of nonobese patients, p-value 0.44.

**Discussion**: Obese women were less likely to have undergone correct cervical cancer screening compared to nonobese patients. Amongst obese patients, morbidly obese women were even less likely to have been correctly screened for cervical cancer and were subsequently more likely to present with symptoms of cervical cancer. Decreased screening for cervical cancer amongst obese women may be secondary to healthcare barriers faced by obese patients. These barriers may include patient shame and fat stigma amongst healthcare providers, as well as physical limitations that hinder these patients from accessing care.

## NEURAL CORRELATES OF POSITIVE AND NEGATIVE AFFECT IN OLDER ADULTS: A STRUCTURAL MRI STUDY

Ashten Sherman<sup>1,3</sup>, Eric Axelson<sup>2</sup>, & Natalie L. Denburg<sup>3</sup> <sup>1</sup>University of Iowa (UI) Carver College of Medicine (CCOM) <sup>2</sup>Department of Psychiatry, UI CCOM <sup>3</sup>Department of Neurology, UI CCOM

<u>BACKGROUND</u>: A striking aspect of human emotion is the variability from person to person. It is believed that such individual differences arise from two dimensions of affect, namely, positive affect and negative affect. Positive affect is defined as the extent to which a person experiences positive moods, while negative affect is the extent to which a person experiences negative moods. In addition, positive and negative affect have been found to be strong predictors of several health outcomes. For instance, a higher level of positive affect has been associated with lower morbidity and decreased pain; by contrast, a high level of negative affect has been associated with greater depression. It is less clear how trait positive and negative affect impact the brain, particularly the aging brain.

<u>AIMS</u>: We sought to explore the neural correlates of both positive and negative affect in older adults using a structural magnetic resonance imaging (MRI) of the brain approach. In addition, we took advantage of previously obtained psychometric data to investigate the relationship between affect and various demographic and cognitive variables.

<u>PARTICIPANTS</u>: Forty community-dwelling older adults (Mean Age = 73.8; SD = 5.5; Range: 60-88 years) took part in the study. All participants were neurologically healthy, and medical status was confirmed with a semi-structured interview.

<u>METHOD</u>: Participants received a 3 Tesla structural brain MRI and completed the Positive and Negative Affect Schedule (PANAS; Watson & Clark, 1994), a self-report measure. All participants had previously completed and passed a comprehensive battery of neuropsychological measures designed to exclude those with cognitive decline.

<u>**RESULTS</u>**: After implementing a stringent correction for multiple comparisons (i.e., false discovery rate), several significant relationships were observed: positive affect was negatively correlated with cortical brain thickness, while negative affect was positively corrected with cortical brain thickness. Most of these relationships involved anterior brain regions in the left hemisphere.</u>

<u>DISCUSSION</u>: Overall, our results showed consistent findings in regard to cortical thickness relationships with positive affect and negative affect. Our findings of positive affect being negatively correlated with cortical thickness and negative affect being positively correlated with cortical thickness are counterintuitive yet consistent with Michalski et al.'s (2016) results from a large (N = 879) young adult sample. One possible interpretation is that increased cortical thickness may be a preexisting vulnerability factor that influences one's perception of the world and creates individual differences in the experience of positive and negative affect.

## EyePrint PRO 3-D Scanned Scleral Contact Lenses: Primary Indications, Visual Outcomes, and Complications

Joanna I.M. Silverman, B.A., Christine W. Sindt, O.D., M. Bridget Zimmerman, Ph.D., and Mark A. Greiner, M.D.

**BACKGROUND:** Scleral contact lenses (SCL) are rigid, gas-permeable, large diameter contact lenses that rest on the sclera and vault over the cornea, creating a protective barrier between the ocular surface and posterior aspect of the lens. SCLs are particularly successful in correcting visual acuity and surface irregularities in patients who are unable to tolerate traditional contact lenses or fail alternative therapies. The EyePrint PRO (EPP) is a novel SCL created at the University of Iowa Department of Ophthalmology and Visual Sciences that uses a 3-D scanned, positive impression polyvinyl siloxane mold of the ocular surface to provide a customized and enhanced fit. Previous studies report benefits of SCL and EPP lenses as non-surgical alternatives to enhance vision and stabilize the ocular surface. However, despite its commercial availability, there exist no large-scale systematic reports of EPP use, outcomes, and complications in patients. We aimed to conduct to a retrospective observational study to evaluate the primary indications, safety, and outcomes of patients fitted with EPP lenses. This retrospective study will provide novel insights necessary for the safe and efficacious use of EPP devices in clinical practice.

**PURPOSE:** To determine the primary indications, outcomes, and complications in patients fitted with EyePrint PRO scleral contact lenses.

**METHODS:** A retrospective medical chart review was conducted to identify all patients at the University of Iowa Hospitals and Clinics who were fitted with EPP SCLs between December 2013 and March 2018. Medical records were reviewed for patient demographics, primary indications for fitting, cessation of lens use, repeat fitting, and previous contact lens use. All patients were followed for the duration of their charted EPP use. The primary outcome measures included best corrected visual acuity (BCVA) measured at initial, intermediate, and final follow-up visits, and complications of contact lens use. Visual acuities were converted to log MAR scale for statistical analysis. Significant differences between BCVA before and after EPP fitting were determined by Wilcoxon sign ranked test. This study was approved by the Institutional Review Board of the University of Iowa Hospitals and Clinics and adhered to the tenants of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act.

**RESULTS:** In this study, 89 eyes from 70 patients included for analysis were fitted with EPP SCLs and followed for a median 11.1 months (IQR 4.4-18.6). Two patients did not complete follow-up. Median age at fitting was 52.2 years (IQR 35.5-63.3) and 46 (66%) patients had previously used contact lenses. The primary indication for the majority of eyes fitted with EPP SCLs was irregular corneal shape (66%). The remaining patients had EPP SCL use indicated for corneal surface disease (17%), exposure keratopathy (10%), neurotrophic keratitis (9%), conjunctival or scleral abnormalities (9%), and corneal scarring (4%). BCVA improved from a baseline of 0.63 (20/85; IQR 0.40-1.18) to 0.03 (20/21; IQR 0.00-0.23; p<0.0001). Median time to 1-line and 4-line BCVA improvement was 1.2 (IQR 0.7-1.8) and 1.8 (IQR 0.9-16.7) months, respectively. Thirty-four (49%) patients developed complications while device cessation occurred in 8 (11%) patients. Neither outcome was associated with prior contact lens use or primary indication (p=0.74, p>0.99). The cumulative probability of device cessation was 17.5% (95% CI: 8.4%, 34.4%) at 18 months, and the rate of cessation was not associated with previous contact lens use or primary indication. Patients who required reprinting of EPP lenses (19%) were more likely to stop lens use than patients who did not (81%; p=0.034).

**CONCLUSION:** EPP SCLs were worn successfully in patients within a wide age range, varying primary indication diagnoses, and history of prior contact lens use. The device resulted in successful improvement in BCVA in most patients. While nearly half of all eyes developed complications of wear during EPP use and approximately one-tenth of patients halted use, neither event was associated with prior contact lens use or primary indication. These data suggest that EPP wear successfully improves visual outcomes and EPP wear should not be precluded as an intervention on the basis of prior lens use or ophthalmic diagnosis. EPP lens reprinting may be predictive of ultimate device failure, which suggests that this device may not be suitable for patients with rapidly unstable ocular surfaces.

## The association between *MMP9* risk alleles and exudative age-related macular degeneration (wet AMD)

Allie Simpson, Elliott Sohn, Robert F. Mullins, Edwin M. Stone, Todd E. Sheetz, Ben R. Roos, John H. Fingert

## Background

Age-related macular degeneration (AMD) is one of the leading causes of blindness in the elderly. Further classification of AMD into exudative (or "wet" AMD) and non-exudative (or "dry" AMD) has prognostic value, as those with wet AMD typically have more advanced disease with severe vision loss. A study by Fritsche et al. (*Nature* 2016) identified the first genetic association specific to wet AMD located near the *MMP9* gene via a whole genome single nucleotide polymorphism (SNP) analysis. The group reported a four base pair deletion at the *MMP9* locus that confers risk for exudative AMD, which might also provide valuable information about prognosis and therapeutic options.

## Purpose

The goal of the study was to better characterize the *MMP9* risk allele in AMD patients from the University of Iowa.

## Methods

We first assessed the *MMP9* risk allele with PCR amplification followed by polyacrylamide gel electrophoresis (PAGE) to determine which AMD patients and control subjects (257 AMD, 219 controls) carried the four base pair deletion at this locus (rs142450006, TTTTC/T). We used Sanger DNA sequencing to confirm findings from PAGE in 12 University of Iowa AMD patients. We further assessed the *MMP9* locus for an association with wet AMD by genotyping 1,538 AMD patients (1,058 wet, 480 dry) at SNPs near the *MMP9* locus (rs4810482, rs17577).

## Results

Our analysis of the *MMP9* risk locus did not detect the previously reported four base pair deletion. Instead we discovered a highly polymorphic four base pair repeat sequence with a variable number of repeats among patients, with greater than 9 different alleles (numbers of repeats) identified (p>0.05). There was not a significant difference in repeats between wet AMD, dry AMD, and controls. Data from the SNP genotyping portion of the study showed that among University of Iowa AMD patients the *MMP9* rare variants (rs4810482, rs17577) between wet and dry AMD were significant (p<0.05).

## Conclusion

A previous report suggested that a *MMP9* risk allele, a four base pair deletion (rs142450006, TTTTC/T), was associated with wet AMD. An *in silico* approach (SNP imputation) was used to infer genotypes in this previous report, rather than using laboratory methods to obtain actual genotypes. Our analysis demonstrates that the polymorphism (rs142450006, TTTTC/T) is actually a short tandem repeat polymorphism (CTTT)n with many alleles. While the *MMP9* locus may still confer risk for wet AMD, it is not due to the variant reported by Fritsche et al. Further research into the significance of the *MMP9* is needed.

#### Effect of Religiosity and Spirituality on Infertility Quality of Life Measures (FertiQoL) in the Infertile Veteran Population Mary Kate Skalitzky, Ginny Ryan, MD

### Background

One under acknowledged challenge for Veterans is infertility. Infertility results in negative medical and psychosocial stressors that reduce overall life satisfaction, marital satisfaction, treatment duration, and treatment success. Assessing quality of life (QoL) of infertile Veterans, as well as factors that mediate QoL, is essential to improve patient satisfaction and treatment outcomes. Existing literature demonstrates that religiosity and spirituality (R/S) can enhance coping, quality of life, and mental health outcomes in diverse patient populations; these associations have not been investigated to date in the infertile Veteran population. Therefore, the goal of this study is to investigate the impact of religiosity and spirituality on quality of life metrics in an infertile Veteran population.

### Hypothesis

Within the infertile Veteran population, higher spirituality and religiosity are associated with higher quality of life metrics, as measured by the FertiQoL tool.

### Aims

- 1. To assess quality of life using FertiQoL in an infertile Veteran population
- 2. To investigate the impact of religiosity and spirituality on QoL metrics
- 3. To investigate the mediating effect of personal and familial resilience on the relationship between R/S and QoL outcomes.

### Methods

Data were collected as part of a larger ongoing study looking at infertility in US military Veterans. Veterans were selected randomly from the VA Defense Information Repository and invited to participate in a 90-minute computer-assisted telephone interview (CATI). The interview included question modules on demographics and general health, military history and combat-related trauma, adverse events in childhood, sexual assault and PTSD, infertility and reproductive history and health, environmental exposures, and resilience and R/S. For all Veterans, resilience was measured by the Connor-Davidson 2 Measure Index and the Family Resilience Scale for Veterans. PTSD was measured dichotomously and with the PCL-5, a validated measure of PTSD symptomatology. The FertiQol quality of life metric was asked only of Veterans who endorsed infertility through one of several measures. The FertiQol metric is an internationally validated tool designed to evaluate quality of life outcomes specifically for individuals suffering from infertility and includes subscales for Emotional, Relational, Mind-Body, and Physical wellbeing. Initial data analysis was completed, including Pearson's correlation to assess the correlation between resilience scales, deployments, and FertiQol score. Univariate analysis was also completed to evaluate factors predictive of FertiQol scores. Model diagnostics were checked to ensure assumptions of linear regression were valid for this data set.

#### Results

We assessed 189 veterans in this interim analysis. The mean FertiQol score was 93.0, which was higher than average scores reported in the literature. The Connor Davidson 2 Index measure of personal resilience was found to be significantly and positively correlated with all FertiQol subscales except the Mind-Body Subscale. The PCL-5 measure of PTSD severity was found to be significantly and negatively correlated with FertiQol subscales, except Social. There was no correlation between the score on the Veteran Family Resilience Scale or with number of Veteran deployments with FertiQol scores. In the univariate analysis, females and veterans with PTSD diagnoses were found to have lower scores than their counterparts. Additionally, only some components of the religiosity and spirituality scales were significant at predicting FertiQol scores, with higher R/S predicting lower scores. In the univariate analysis, the Connor-Davidson index was also found to be positively predictive of FertiQol scores.

#### Conclusions

Because so many veterans scored so highly on FertiQol scores, we may not be able to effectively differentiate between Veterans. While R/S may not be protective as we had hypothesized, potentially due to the higher FertiQol scores, this study indicates the value of resilience for this infertile Veteran population. The Connor-Davidson 2 index is a useful measure for healthcare providers looking to predict quality of life for their infertile Veteran patients. Furthermore, the data suggests that enhancing resilience may prove to be an effective mechanism of improving quality of life indicators for this population. Additionally, PTSD diagnosis was found to be negatively correlated with quality of life outcomes. Prevention and management of PTSD are also important tools for enhancing outcomes for these Veterans.

## Does Iatrogenic Cartilage Injury Risk Damage to Otherwise Healthy Chondrocytes Overlying Cam Morphology? Michael Slattery BA, Jocelyn Compton MD Mentors: Mitchell Coleman PhD & Robert Westermann MD

Introduction: Cam-type femoroacetabular impingement (FAI) is a condition in which extra bone and cartilage growth occurs on the anterolateral femoral head-neck junction, causing abnormal contact between the femur and the acetabulum. FAI causes hip pain in younger patients and early onset of osteoarthritis (OA). Current surgical interventions for FAI show good short-term outcomes with symptom relief and increased functionality. However, older patients or patients with pre-existing OA fail to improve symptomatically more frequently than younger counterparts. Autologous chondrocyte implantation (ACI) has been implemented to combat OA in the knee and may be beneficial for these FAI patients. In this procedure, a small piece of cartilage is removed from the knee and healthy chondrocytes are isolated and expanded ex vivo. A chondrocyte-rich implant is then created and placed on lesioned articular cartilage via a second surgery. A similar procedure done arthroscopically might utilize tissue from the cam overgrowth to seed lesions within the hip at a later surgery. To our knowledge, ACI has not yet been conducted in the hip.

<u>Aim:</u> The aim of our study is two-fold. 1) Investigate whether chondrocytes isolated from cam lesions in FAI patients are metabolically similar to normal chondrocytes and therefore a viable option for ACI in FAI patients with OA. 2) Examine the effects of iatrogenic cartilage injury during arthroscopy on healthy chondrocytes to identify potential risk of damage to the chondrocytes during procurement for ACI.

<u>Methods</u>: To investigate the metabolic activity of chondrocytes overlaying cam lesions, cam cartilage was obtained intraoperatively from 7 human patients radiographically identified as having cam lesions (4 arthroscopy, 2 arthroplasty, and 1 periacetabular osteotomy). Healthy femoral and acetabular articular cartilage was obtained from 8 Yucatan minipig hips donated by the Goetz lab to be used as an animal model comparison for healthy chondrocytes. Chondrocytes were extracted from the cartilage using 0.1 mg/mL collagenase and pronase in media then cultured at a high density for up to 1 week without passaging. A Seahorse Bioscience XF96 Extracellular Flux Analyzer was used to assess mitochondrial function using standard mitochondrial stress testing procedures (with 2  $\mu$ M oligomycin, 2.5  $\mu$ M carbonyl cyanide p-trifluoromethoxy-phenylhydrazone (FCCP), 2  $\mu$ M rotenone, 5  $\mu$ M antimycin A) for determination of the chondrocytes basal and maximal respiration. To investigate iatrogenic cartilage injury, a conical arthroscopic trochar was used to create minor iatrogenic injuries to bovine femoral condyle explants. Varied masses were used during injury to mimic minor (1.5 N), intermediate (2.5 N) and major injury (9.8 N). The explant was incubated in 0.9% normal saline for 2 hours at 37°C to replicate a 2-hour procedure. Samples were incubated with 1  $\mu$ M ethidium homodimer-2 and imaged via Olympus FV1000 confocal microscope at 535 nm wavelength.

<u>Results:</u> No significant differences in basal or maximum respiration were found when comparing chondrocytes from cam lesions to normal porcine femoral articular cartilage (p = 0.7303 & p = 0.3994, respectively). There was a significant difference in maximum respiration when comparing chondrocytes found on cam lesions in patients who underwent a total hip arthroplasty to chondrocytes found on other cam lesions (p = 0.007). However, when comparing the basal respiration of these groups, measurements have not yet reached statistical significance (p = 0.24). Cell death from trochar contact with articular cartilage was assessed at three forces (1.5 N, 2.5 N, and 9.8 N). Each level of force showed significant death evenly across the path of the trochar. The highest force, (9.8 N) showed increased width of injury compared with the smaller forces (1.5 and 2.5 N), p = 0.01758.

<u>Discussion</u>: Basal and maximum respiration in chondrocytes obtained from cartilage overlying cam lesions via arthroscopy or PAO suggests a similar level of respiration to healthy articular chondrocytes obtained from Yucatan minipig hips. We believe this provides evidence of a potential novel chondrocyte source to be used for ACI in cam-type FAI patients. It is important to note that older patients with OA present showed a significant increase in respiration in line with published data from arthritic knees. This may suggest that chondrocytes from later stage patients might not function optimally in an ACI approach; however, only two patients were accrued for this group and additional replicates will be needed. The cellular death seen in our iatrogenic cartilage injury model provides reasoning for extra caution when potentially procuring cartilage arthroscopically for ACI. Scuffing the cartilage with arthroscopic tools, even at small forces (1.5 N), could reduce viable chondrocyte numbers or even initiate extracellular catabolic cascades activated by cell death. Future studies will assess whether these cascades are initiated in and around this in vitro scratch with the intention of developing an in vivo model of iatrogenic cartilage injury-induced joint pathology.

## **Endocrine Effects of BPF on HS Rat Lipids**

Ryan Staudte, Valerie Wagner, Karen Clark, Leslie Saenz, Anne Kwitek

### Background

Bisphenol F (BPF) is marketed as a "safe" substitute for Bisphenol A (BPA), an established xenoestrogen endocrine disruptor. BPF is used in epoxy resins and coatings (e.g., lacquers, varnishes, food packaging and can liners, adhesives, water pipes, and dental sealants). Studies suggest BPA is involved in metabolic syndrome (MetS), including obesity, hyperlipidemia, and hyperglycemia. Given its structural homology to BPA, BPF might also contribute to similar features of MetS. Previous BPF studies have been understudied *in vivo* and performed only in genetically undefined or inbred mice and rat populations.

## **Purpose of the Study**

The main aim of this pilot project was to see if BPF induces obesity, dyslipidemia, or hyperglycemia in a similar manner to BPA.

## Methods

<u>Rats</u>: Heterogeneous Stock (HS) rats that had been bred for 80+ generations were purchased from Dr. Leah Solberg-Woods of Wake Forest University. The HS rat was made in the 1980's by the NIH to serve as a model that mimics the diversity of the human population. Offspring from eight parent strains of the HS rat were mixed to minimize inbreeding and maximize diversity.

<u>Exposure</u>: Male HS rats weaned at day 21 (3 weeks) were fed *ad libitum* on a phytoestrogen-free diet (Teklad 2920X), housed in bisphenol-free polypropylene caging, and given either water containing 1.125mg/dL of BPF dissolved in 0.1% ethanol, or vehicle control (0.1% ethanol) via glass bottles. The rats were weighed and their body growth measured weekly. Non-fasting blood glucose was determined at weeks 3 and 8. At 8 weeks of age, rats were euthanized via CO2 and thoracotomy. Fasting serum was collected along with tissues (e.g., liver) that were snap frozen.

<u>Analysis</u>: Serum and liver triglycerides and serum cholesterol were quantified with colormetric cholesterol and trigylceride kits (BioAssay Systems). A linear mixed model regression was used to estimate heritability and identify significant influences of BPF exposure.

## Results

Our preliminary data suggests BPF did not significantly impact cholesterol, triglyceride, or fasting blood glucose levels. However, BPF did increase body fat as measured by NMR (p = 0.0573) and visceral adipose tissue, nose-rump body length, and gain in body weight since wean all are significantly larger in the treated group versus the control (p<0.05).

Intraclass correlation values (as a rough estimate for heritability) in each individual treatment and control group (lacking Group fixed effect) show a high level of estimated heritability (>0.90) but when Group fixed effect is included in the calculation, the ICC is much lower (~0.50).

## Discussion

Our preliminary results suggest that BPF at the dose we studied has no effect on inducing dyslipidemia or hyperglycemia; it must be noted there was insufficient power to reject or accept the null hypothesis. However, there was a significant effect of BPF on body weight and adiposity, suggesting BPF influences MetS in rats. Other effects such as increased adipogenesis have been documented in BPA-rat studies. Significant findings of increased growth may suggest that BPF may upregulate somatotroph activity as BPA has been shown to concentrate heavily in the pituitary gland. Given that enterohepatic cycling may cause BPF levels to remain in rats longer, an equivalent dose in humans would be expected to have even less effect as humans. In humans, bisphenols (BPA) have been shown to be rapidly glucuronidated (inactivated) in the liver and excreted in the urine. The heritability estimates by ICC suggest that BPF exposure may contribute to the GxE interactions, but further analyses utilizing the family tree of HS rats will better address possible interactions between genes influencing MetS and BPF exposure.

## **Refining a Mind-Controlled Robot: Bispectral feature extraction improves brain-computer interface performance**

Contributors: Danial Syed, Dr. Matthew Howard, Dr. Christopher Kovach

Brain-computer interfaces (BCIs) allow a computer to interpret and act on its user's intentions, without need of the peripheral nervous system. BCIs classify brain states by extracting relevant features from electrode data and classifying intention through machine learning techniques. Time-varying signal power, recovered by bandpass filtering within pre-selected frequency bands, often provides the input to such classifiers. But because the power spectrum discards phase information, these techniques are insensitive to properties of the signal related to spectral phase, such as information encoded in cross-frequency interactions, notably phase-amplitude coupling. This information is preserved in so-called higher-order spectra, which are related to time-shift invariant higher moments.

We have recently described a novel technique for recovering information from higher-order spectra using an application of the bispectrum (Kovach et al. 2018, Kovach and Howard, submitted), in the form of filters optimized for the detection of characteristic recurring signal features. Here, we investigated whether this bispectral approach to feature extraction could improve the performance of an electrocorticographic (ECoG) BCI. We trained a support vector machine classifier to discriminate two mental task conditions (in which a human subject was instructed to "imagine the tune of 'Jingle Bells'" or "imagine feeling very angry"), using both bandpass power in standard EEG frequency bands and the output of bispectral feature extraction. The trained classifier was used offline to simulate driving a robot in real time.

Our bispectral/bandpass classifier performed with higher accuracy than either technique alone. Additionally, the combined classifier performed comparably to band power alone using fewer channels. Our findings suggest that feature identification with higher-order spectra may improve ECoG BCI performance while minimizing implant size.

## Preferences for Emergency Medical Service Transport After Childhood Injury: An Emergency Department-Based Mixed Methods Study

Robert Thinnes, BS<sup>1</sup>, Morgan Swanson, BS<sup>2, 3</sup>, Karisa Harland, PhD, MPH<sup>2, 3</sup>, Nicholas Mohr, MD, MS<sup>2, 3, 4</sup> <sup>1</sup>University of Iowa, Carver College of Medicine <sup>2</sup>University of Iowa, College of Public Health, Department of Epidemiology <sup>3</sup>University of Iowa, Carver College of Medicine, Department of Emergency Medicine

<sup>4</sup>University of Iowa, Carver College of Medicine, Department of Anesthesia Critical Care

### Background

Pre-hospital ambulance transport is associated with shorter time to definitive care and fewer subsequent inter-hospital transfers. However, greater than 35% of pediatric trauma patients arrive to an ED without using EMS. The objective of this study was to elucidate guardians' decision factors in determining mode of transport for their child following an injury.

## Methods

This is a mixed methods study of a purposive sample of pediatric trauma patients (≤14 years) and their legal guardians presenting to the ED of an academic level I pediatric trauma center via both EMS and non-EMS modalities. Demographic information for children and guardians was collected, and injury characteristics, location of residence, and family factors were recorded. Semi-structured interviews were conducted, audio recorded, and transcribed for thematic content analysis based in grounded theory. Two reviewers independently identified qualitative codes and assigned codes into themes based on a consensus of experts.

## Results

Twenty-eight child-guardian pairs were enrolled. The median age of pediatric participants was 7 years (IQR 3 - 11 years). Thirteen participants (46.4%) presented to the initial hospital by EMS. Eighteen participants (64.3%) were admitted to the inpatient floor. Among guardians, eleven (39.3%) reported prior use of an ambulance for their own medical care.

Three major themes emerged from the interviews: perceived injury severity drives EMS use, cost was not a major factor in guardians' decision for mode of transport, and most guardians were unfamiliar with local EMS capabilities. Generally, guardians consider EMS use to minimize risk to their child when bleeding, loss of consciousness, or severe injuries are involved. While previous reports have cited cost as important in parent decision-making, in our study, guardians cited cost to be a risk of EMS use, but few cited this as a factor contributing to their decision-making. Finally, guardians cited lack of familiarity related to the capabilities, roles, and response times of their local EMS providers.

## Conclusions

Physical signs of injury and minimizing risk were important decision factors used by guardians after a child's injury. Future direction should compare outcome differences between EMS use and non-use in pediatric trauma.

## DISPOSITIONAL MINDFULNESS IN HEALTHY OLDER ADULTS IS ASSOCIATED WITH CORTICAL THINNING IN THE BRAIN

H.E. Trembath<sup>1</sup>, A.I. Roche<sup>2</sup>, X. Chen<sup>1</sup>, & N.L. Denburg<sup>1</sup>,<sup>2</sup>

<sup>1</sup>Department of Neurology, University of Iowa Carver College of Medicine <sup>2</sup>Department of Psychological and Brain Sciences, University of Iowa

## ABSTRACT

**BACKGROUND**: Mindfulness is the state of being aware and attentive to the present moment without judgment. Mindfulness is conceptualized in two ways, as cultivated (via meditation or mindfulness-based intervention) mindfulness and dispositional (trait) mindfulness. There are a limited number of studies exploring the structural correlates of dispositional mindfulness generally, and while many areas of the brain have been identified as potentially related to dispositional mindfulness, there is no consensus in the field. More specifically, to our knowledge, no study to date has explored the structural correlates of dispositional mindfulness of dispositional mindfulness.

**AIMS**: We sought to explore the neural correlates of dispositional mindfulness in older adults using a structural magnetic resonance imaging (MRI) of the brain approach.

**METHODS:** Forty-three healthy, community-dwelling older adults (*Mean age* = 74.4, SD = 5.7; *Median age* = 74 years, range 60-88) completed neuropsychological evaluation, several self-report dispositional mindfulness measures, and structural neuroimaging of the brain. We correlated dispositional mindfulness with MRI- derived cortical thickness measurements.

**RESULTS**: Analysis revealed several significant relationships between dispositional mindfulness and cortical thickness, after controlling for age and after utilizing a strict correction (Monte Carlo simulation) to control for Type I error inflation (i.e., false positive findings). Interestingly, all of these obtained relationships were negative, i.e., higher dispositional mindfulness was related to greater cortical thinning.

**CONCLUSIONS**: Several relationships were observed and all findings were negative correlations, meaning higher trait mindfulness was associated with thinner regions of the brain. This is in contrast to the well-documented positive correlation of cultivated mindfulness with increased regional cortical thickness. We discussed our findings in the conceptualization that mindfulness is a broad and multifaceted psychological construct with cultivated and dispositional mindfulness being related but distinct entities.

### The Effect of Resilience and Depression on Outcomes After Total Hip and Knee Arthroplasty

Jonathan Trinh, Jesse E. Otero M.D. Ph.D., Nicolas Noiseux M.D., Timothy S. Brown M.D.

#### Background

Current patient optimization protocols for total joint arthroplasty include encouraging patients to stop smoking, maintain a body mass index of  $< 40 \text{ kg/m}^2$ , and keep Hemoglobin A1c levels below 8.0%. However, more research needs to be done to evaluate if different psychological or mental health-related factors can affect outcomes for these procedures.

### **Purpose of the study**

Through a prospective study of patients undergoing total hip or knee arthroplasty, we aim to understand the relationship between resilience and depression as well as their effect on outcomes. The specific questions we will explore include:

- 1) What is the level of resilience of patients undergoing primary THA or TKA?
- 2) How does baseline resilience affect clinical outcomes after THA and TKA?
- 3) What is the incidence of depression in patients undergoing THA and TKA?
- 4) How do depression levels change over various follow-up postoperative intervals?

We hypothesize that resilience has a positive correlation with good clinical outcomes after total joint arthroplasty while depression has a negative correlation with them. We also expect to find that patients' depression levels should decrease after their surgeries.

### Method

193 patients scheduled for primary total hip or knee arthroplasty by one of three surgeons (JO, NN, TB) in the Department of Orthopedics and Rehabilitation at the University of Iowa consented to participating in the study. Patients filled out two questionnaires at a pre-operative appointment. To measure resilience, patients filled out the Brief Resilience Scale (BRS). To measure depression, patients filled out the PHQ-9. The patients will then complete the PHQ-9 again six weeks to three months after the surgery as well as one year after the surgery. Scores for both scales were analyzed using basic statistical descriptors, such as mean, median, and range. Clinical outcome and quality of life postoperatively will be measured using the PROMIS10 and HOOS Jr or KOOS Jr scores.

#### Results

As a prospective study, outcome data will be obtained with standard clinical follow up over the next 2 years. However, the preoperative data answers some of our specific aims and also gave insight into what a population undergoing total joint replacement looks like. Of the 193 patients, 95 will receive total hip replacements (49.2%) and 98 total knee replacements (50.8%). 102 were female (52.8%), and the average age was 61.0 with a standard deviation of 11.5. The average BRS score was a 23.5 out of 30 with a standard deviation of 4.4. 36 (18.6%) were classified as high-resilience (28 points or higher) and 31 (16.0%) were classified as low-resilience (19 points or lower). The median PHQ9 score was 4 out of 27. However, 29 (15.0%) patients fell into the "moderate depression" category and 7 (3.6%) into the "severe depression" category. Additionally, linear regression of patients' BRS and PHQ9 scores demonstrated a trend that more resilient patients tended to be less depressed.

## Conclusion

The pre-operative data indicates that the population of patients undergoing primary hip or knee replacement includes a wide range of levels of resiliency and depression. For instance, while the median score on the PHQ9 was 4, which indicates depression severity of "none-minimal," 47 of the 193 patients (24.3%) had at least moderate depression. Results over the next year will reveal if someone's level of resilience impacts their outcomes and if depression scores change following surgery.

## Quality of Treatment for Clubfoot Deformity: A Decade Analysis of Patient-centered Care Victoria L Troesch, BS\*, Sarah M. Dougherty, BS\*, Asitha DL Jayawardena, MD, MPH, Thomas Cook, Phd, Qiang An, Jose Morcuende, MD, Phd

#### Background:

Previous views of paternalistic medicine are shifting to embody a more patient-centered approach to treatment. One group that is at the forefront of this transition is the clubfoot community. Clubfoot is the most common musculoskeletal birth defect worldwide, which results in increased morbidity due to decreased mobility and increased risk for bone and skin infections. The Ponseti method is the gold standard of treatment for clubfoot and requires compliance to a strict and long 4-year bracing protocol. The physician and parent relationship must be especially transparent here, as understanding of how to correctly wear braces is vital to prevent relapses and ensure full correction of the deformity. Quality educational material and patient-centered care are paramount to successful patient outcomes.

#### *Purpose of the study:*

The goal of this study was to provide a thorough analysis of the last decade to help shed light on the quality of care in the clubfoot community and any changes that may have ensued.

#### Methods:

A survey was distributed online on active clubfoot support groups in 2009, 2012, and 2018. Main domains of questions included: respondent characteristics, information sources about the Ponseti method, treatment specifics, perceptions of physician competence, and perceptions regarding quality of care.

#### Results:

There were a total number of 927 responses to the survey throughout the years, with 276 of them coming from the 2018 survey. In 2018, approximately one-third of the respondents were international, representing 33 different countries. Compared to patients that didn't report substandard care, patients that reported substandard care were more likely to also switch physicians (p<0.0001), not immediately be given information about clubfoot upon diagnosis (p=0.0104), first learn of the Ponseti method from personal research rather than from a medical professional (p=0.0011), consult more physician's after treatment began (p<0.0001), have more physician's apply casts (p<0.0001), experience a relapse (p<0.0001), and self-refer to a physician (p<0.0001). These trends have remained consistent each time we have given the survey. Improvements throughout the last decade have been minimal.

#### Conclusions:

Patient education is essential in the Ponseti method, and the data shows many aspects of care that are deemed inadequate and substandard by parents. Although there were some improvements throughout the last decade, the numbers of patients switching doctors and experiencing substandard care are still high. Parents should be receiving a higher quality of education from medical professionals regarding their child's clubfoot condition.

## Staphylococcus aureus Nasal Carriage and the Risk of Surgical Site Infections among Patients Undergoing Orthopedic Surgical Procedures to Fix Acute Fractures: A Retrospective Cohort Study

<u>Contributors</u>: Richard Uhlenhopp, BS, Jocelyn Compton, M, Michael Willey, MD, Melissa Ward, MS, Marin Schweizer, PhD, Loreen Herwaldt, MD

<u>Background:</u> The incidence of *Staphylococcus aureus* (SA) nasal carriage and outcomes associated with carriage have not been well defined in the orthopedic trauma patient population. Since early 2014, orthopedic trauma patients admitted to the University of Iowa Hospitals and Clinics' (UIHC) have been screened for SA nasal carriage and carriers have been prescribed a decolonization protocol that includes applying mupirocin to their nares in the preoperative period and vancomycin for perioperative prophylaxis.

## Purpose:

The study aims were to: 1) determine the incidence of methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) carriage in the study population; 2) determine adherence rates for treating carriers with intranasal mupirocin; 3) assess if *S. aureus* nasal carriage increased the risk of *S. aureus* SSI in this patient population.

## Methods:

We conducted a retrospective cohort study of consecutive patients who underwent surgical procedures done by any of three orthopedic traumatologists at the UIHC from 8/1/2014 - 7/31/2017. We collected 75 data points, in three main categories: patient factors, surgery/treatment factors, and SSI. We reviewed patients' electronic medical records from the time of their operations through their most recent clinic appointments with a traumatologist and abstracted relevant data. We used two definitions of SSI: CDC's National Healthcare Safety Network's definition and any SSI diagnosed by an orthopedist during follow up (surgeon's definition). For the analyses, we used two-sample t-tests for continuous variables, chi-squared and Fisher's exact tests for categorical variables, and logistic regression for multivariable analyses.

## Results:

Of the 1257 total patients, 1003 (79.8%) were screened, 200 (19.9%) of whom carried MSSA and 48 (4.8%) carried MRSA. Of the patients who carried SA, 40.9% received mupirocin. None of the factors we assessed were associated with MSSA carriage or with MSSA SSI. Diabetes and long-term care facility (LTCF) residence were significantly associated with carriage of any SA while age, BMI, diabetes, heart disease, and LTCF residence were associated with MRSA carriage. For both SSI definitions, alcoholism and MRSA carriage were significantly associated with MRSA SSI. After adjusting for clinically and statistically significant variables such as age, BMI, closed fracture, ISS category, alcoholism, and tobacco use, MRSA nasal carriage remained strongly associated with SSI (OR; 95% CI): All SSI (CDC; 2.75 [1.01-7.48]), MRSA SSI (CDC; 19.81 [5.22-75.18]), all SSI (surgeon's; 2.62 [1.15-5.95]), MRSA SSI (surgeon's); 16.53 [4.61-59.22]).

## Conclusions:

At a single, Midwestern, tertiary-care facility the nasal MSSA and MRSA colonization rates among orthopedic trauma patients were 19.94% and 4.8%, respectively. MRSA colonization was the variable most significantly associated with all SSI and with MRSA SSI as defined by either CDC or the surgeons. MRSA colonization was also the only modifiable risk factor for these SSI. Given the low mupirocin adherence rate (40.9%), we suggest testing an easier alternative for decolonization, such as intranasal povidone-iodine, which can be applied immediately before the operation.

#### Investigating the Link Between PKA Regulation and Late-Onset Neurodegeneration

Justin Valdez<sup>1</sup>, Marie Gaine<sup>2,3</sup>, Ted Abel<sup>1,2,3</sup>

<sup>1</sup>University of Iowa Carver College of Medicine, <sup>2</sup>Iowa Neuroscience Institute, <sup>3</sup>Department of Molecular Physiology

and Biophysics

**Background:** Protein kinase A (PKA) is an essential enzyme for the regulation of neuronal function and is mediated by different regulatory subunits. PKA is a heterotetramer, consisting of two regulatory subunits and two catalytic subunits. The binding of cyclic AMP to the regulatory subunits releases the catalytic subunits and enables PKA signaling (Wong et al., 2014). The type 1-beta regulatory subunit of the cyclic AMP (cAMP)-dependent PKA holoenzyme is encoded by the PRKAR1B gene (McKusick & Kniffin, 2017). Recently, a novel hereditary neurodegenerative disorder has been found to be associated with a missense mutation in the PRKAR1B gene that involves a unique neuropathological phenotype with PRKAR1B accumulation into abundant neuronal inclusions (Wong et al., 2014). The neurodegenerative disease presented with dementia and parkinsonism as well. The aims of the current study were to investigate if the PRKAR1B mutation alters common markers for neurodegeneration in different ages of mice.

**Hypothesis:** A single nucleotide polymorphism in PRKAR1B alters PKA regulation and causes neurodegenerative– associated phenotypes.

**Methods:** Using CRISPR genome editing technology the single nucleotide polymorphism identified in the PRKAR1B gene was inserted into a mouse model and these mice were subsequently back-crossed to wild-type females. The presence of the mutation was confirmed by Sanger Sequencing. Wild-type (C57BL/6) and PRKAR1B mutant mice of close birth date were subjected to behavioral tests. Neuromuscular coordination and motor skill learning were assessed using the rotarod performance test. Learning and memory were assessed using freeze scan technology during fear conditioning.

**Results:** Learning curves from both the rotarod performance test and fear conditioning test were analyzed by a two-way analysis of variance (ANOVA). A *p* value of <0.05 was considered statistically significant. For the rotarod performance test, the interaction between time and the wild-type (n= 13) and PRKAR1B mutant (n= 8) groups was not significant (p > 0.05). For the fear conditioning test, the interaction between the percent freezing scores of the contextual freezing and the wild-type (n= 11) and PRKAR1B mutant (n= 9) groups was not significant (p = 0.9725).

**Conclusions:** The current preliminary data shows that a missense mutation in the PRKAR1B gene does not significantly impact learning and memory or neuromuscular coordination. However, the current data collected is only from mice ranging in age from 8 to 9 months. Differences may become more present at older ages. The current study is in an infant stage as well and much data has yet to be collected. As far as behavioral data, wild-type and PRKAR1B mice will be subjected to spatial object recognition tests to further evaluate learning and memory and additional data will be collected from rotarod and fear conditioning tests. Furthermore, at ages 8 weeks, 6 months, and 1 year the mice will be euthanized via cervical dislocation and the brains will either be dissected for region-specific RNA/protein or processed for immunohistochemistry.

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## In Vitro and In Vivo Evaluation of DEPDC5 as a Causative Gene for Brugada Syndrome

Hanora Van Ert MSTP M1G, Alex Greiner MSTP M5G, Barry London MD PhD (mentor)

## Background, rationale or introduction

Brugada Syndrome (BrS) is a rare, autosomal dominant, inherited cardiac arrhythmia syndrome that can lead to electrocardiogram (EKG) abnormalities, ventricular arrhythmias and sudden cardiac death (SCD) in people with structurally normal hearts. Approximately 20% of BrS cases are caused by mutations in the cardiac sodium channel, *SCN5A*. Ventricular arrhythmias are precipitated by decreased sodium current in cardiac tissue leading to shortening of the action potential and/or slowing of cardiac conduction velocity. Sudden Unexplained Death in Epilepsy (SUDEP) is a condition in which patients with epilepsy die without evidence of other probable causes. Causal genes associated with SUDEP and epilepsy include the neuronal and cardiac sodium channels *SCN1A, SCN5A*, and *SCN8A*. DEPDC5 is a negative regulator of the cellular regulatory mTORC1 pathway that controls cellular growth by sensing nutrient availability. Mutations in DEPDC5 were identified in families with SUDEP, and a whole exome sequencing study of 61 SUDEP cases revealed that variants in DEPDC5 were associated with SUDEP. Using whole exome sequencing of families with BrS and no known genetic cause, we identified a putative mutation in DEPDC5 (R116L) that co-segregates with the phenotype. We hypothesize that DEPDC5 could be a regulator of sodium channels in both heart and brain tissue, and could be playing a role in the disease mechanism underlying Brugada Syndrome.

## Purpose of the study

To evaluate DEPDC5 as a causative gene for BrS using heterozygous global knockout (Depdc5<sup>+/-</sup>) mouse model.

## Methods

We examined mouse cardiac phenotype by conducting EKGs using subdermal electrodes on Depdc5<sup>+/-</sup> mice and wild type (WT) littermate controls at three months of age, both at baseline and following intraperitoneal injection of the sodium channel blocker procainamide, to elucidate underlying BrS phenotypes. We used qPCR to determine total DEPDC5 mRNA expression level and expression of individual DEPDC5 isoforms. Additionally, we used vector cloning to create plasmids with the WT DEPDC5 and R116L DEPDC5 coding sequences.

## Results

There were no abnormalities suggestive of BrS or arrhythmias on EKG in Depdc5<sup>+/-</sup> mice. Our qPCR experiment revealed a non-significant decrease (~10%) in total DEPDC5 expression in Depdc5<sup>+/-</sup> mice compared to WT mice. Additionally, we examined mRNA expression levels of three protein encoding DEPDC5 isoforms found in mouse cardiac tissue. We saw a non-significant increase (~7%) in DEPDC5 isoform 1 mRNA expression between Depdc5<sup>+/-</sup> and WT mice, a non-significant increase (~50%) for Isoform 2, and a non-significant (~50%) decrease for Isoform 3.

## **Conclusions/Discussion/Future Directions**

The qPCR data showing similar mRNA expression levels of DEPDC5 in both WT and Depdc5<sup>+/-</sup> mice suggests that perhaps the mice are compensating for the loss of one DEPDC5 allele at the mRNA level. We interpret this as meaning that DEPDC5 plays a crucial role in cellular regulation, homeostasis and/or function. Our lab plans to continue to breed the Depdc5 mice to engineer a tissue specific conditional knockout model. Additionally, the DEPDC5 plasmid constructs will be co-transfected with cardiac sodium channels in heterologous expression systems and transfected into cardiac myocytes to determine the effect of both WT and mutant DEPDC5 on sodium currents.
## Using Engineered Photopolymerized Micropatterns and Live Cell Imaging to Study the Growth of Spiral Ganglion Neurons

Joseph Vecchi, Mentor: Dr. Marlan Hansen, Collaborator: Dr. Allan Guymon

#### Background

Inducing better neural growth into cochlear implants is a goal of researchers to improve resolution of hearing from these devices. Cells respond to physical and chemical cues in their growth and migration. It has been demonstrated that physical micropatterns can be used to induce alignment and controlled growth in Spiral Ganglion Neurons (SGNs) in a desired direction. While various chemical signals can inhibit or promote this as well.

#### Purpose

It is known through previous work with SGNs that inhibition of the channel TRPV1 is involved in decreasing alignment phenotype so the agonist of this channel, Capsaicin, was explored. Previous alignment work was done on fixed samples at multiple day time-points, so how certain physical and chemical cues created more alignment or growth is uncertain. Therefore we proposed to use SGNs from a mouse line whose neurons contain YFP (Thy1-YFP) to study them in real time using live cell imaging.

#### Method

Micropatterns that had a periodicity of 20um and feature amplitude of 3-4um were used. The patterns were coupled to glass slides and made from a mix of 40 wt% hexyl methacrylate and 60% wt% 1,6-hexanediol dimethacrylate. The features were made using a photomask and UV light exposure.

Spiral Ganglion Neurons were dissected from Thy1-YFP mouse pups (p3-p5) and plating on the micropatterns with a coating of Poly-D-Lysine and Laminin. Cultures were assessed via live cell imaging at either 24 hours or 48 hours. Capsaicin was added to the culture at 24 hours and then cultures were fixed at 48 hours after capsaicin treatment. Alignment was measured using ImageJ and the ratio of neurite length to straight-line distance of the pattern was calculated.

#### Results

Capsaicin treatment of 10uM and 50uM were explored for this study. The results from a single trial show a modest but inconclusive increase in alignment with a greater capsaicin treatment. The live cell imaging of SGNs could not be made into functional experimental platform. The cells would cease growing and their fluorescence would fade once imaging began. An adequate length of video could not be obtained.

#### Conclusion

Results of these experiments were inconclusive and point to further experiments to consider. The capsaicin study should be repeated and the dose of capsaicin should be increased as well to see if trends hold and strengthen. Live cell imaging of neurite growth could be explored in a heartier cell type such as Trigeminal Neurons if desired.

## Insights into the pathogenesis of leishmaniasis through the study of circulating exosomes

Joyce Wahba<sup>1</sup>, Michael Klemme<sup>1</sup>, Gloria Monteiro<sup>2</sup>, Jose Flavio Vidal Coutinho<sup>2</sup>, Daniella Martins<sup>2</sup>, Mary Wilson<sup>3</sup>, and Selma Jeronimo<sup>2</sup>

- 1 University of Iowa Carver College of Medicine
- 2 Institute of Tropical Medicine of Rio Grande do Norte, UFRN, Natal, RN, Brazil
- 3 Departments of Internal Medicine and Microbiology, University of Iowa

**BACKGROUND:** Visceral Leishmaniasis (VL) is a parasitic disease that is endemic in >90 countries worldwide including Brazil. The parasite causing South American VL, *Leishmania infantum*, primarily uses dogs as a reservoir and sand flies as an insect vector in order to cause disease in humans. Symptoms include fever, weight loss, night sweats, malaise, anemia, and hepatosplenomegaly. The disease has a 90% mortality rate if left untreated. Currently, the gold standard for diagnosis is to visualize the parasite within a bone marrow aspirate, a painful procedure with associated risks (bleeding, infection). As of now, there is a lot to be learned about the pathogenesis of VL including how the parasites cause systemic symptoms and affect gene expression in the cells they reside in, and whether they use secreted vesicles called exosomes to cause disease. Furthermore we don't know whether the content of exosomes could potentially be used in the future as a diagnostic marker to differentiate between symptomatic and asymptomatic disease.

**PURPOSE:** The purpose of this study is to understand the pathogenesis of visceral leishmaniasis and specifically the role of exosomes in disease. We <u>hypothesize</u> that circulating exosomes from subjects with VL may contain parasite proteins that affect the pathogenesis of disease. Furthermore, we hypothesize studies of exosome contents may set up the grounds for generating a new diagnostic tool for leishmaniasis.

**METHODS:** We traveled to Natal, Brazil for 10 weeks where we collected serum from subjects (humans and dogs) with acute VL, after which we extracted and analyzed the exosomes. A chart review was also conducted to gather data on subjects who donated blood for our exosome studied. Proteins were quantified using BCA assay, and RNA/DNA was quantified using nanodrop. Protein analysis was done using ELISA and Western blots.

**RESULTS:** Exosomes were extracted from more than 200 subjects and analyzed. The largest proportion of exosome content seemed to be protein. Indeed, BCA analysis showed that VL+ dogs had the highest amount of proteins as expected. Preliminary western blots showed that there might be a protein unique to sera from subjects with symptomatic VL. Furthermore, there was a trend toward more exosomal protein in samples from patients compared to asymptomatic subjects or control subjects from VL - endemic regions.

**CONCLUSION:** The data is consistent with the hypothesis that exosomes may be an important in the pathogenesis of Visceral Leishmaniasis. This project will continue in Iowa with studies of specific protein content in exosomes, using mass spectrometry, and RNA-sequence analysis of exosomal RNAs.

## Induction of Cell Death by Outer Membrane Vesicles Produced by Neisseria meningitidis

Mackenzie Walhof; Mentor: Jason Barker, MD

*Background*: Lipopolysaccharides (LPS), also commonly referred to as endotoxin for its ability to generate potent inflammatory response in mammalian cells, comprises a large portion of the outer membrane of gram negative bacteria (GNB). A variety of host LPS-recognition systems have been described that generate protective innate immune responses to extracellular LPS. Recently, a novel system – the noncanonical inflammasome - has been described that responds to LPS that has reached the host cell cytosol. Outer membrane vesicles (OMVs), generated by GNB during replication activate the noncanonical inflammasome, but how OMVs deliver LPS to the cytosol is unknown.

*Hypothesis*: We hypothesize that OMVs produced at different phases in bacterial growth display unique structural features which permit trafficking of LPS-rich membranes to the cytosol. We believe OMVs with distinct features will differ with respect to their ability to induce noncanonical inflammasome activation, as measured by cytotoxicity.

*Methods*: An acetate auxotroph of Neisseria meningitidis serogroup B was metabolically radiolabeled during growth in broth. OMVs were harvested from sterile-filtered culture media in both the late logarithmic phase of growth (8 hours) as well as the late stationary phase of growth (18 hours). OMVs were purified in two ways: 1) ultracentrifugation to generate a pellet, and 2) size exclusion chromatography (SEC) to resolve and collect OMVs on the basis of size. Use of H<sup>3</sup>-labeling facilitated analysis of OMV fatty acid contents, permitting normalization for LPS content in OMV. Protein content of OMVs was assessed using binchonic acid assay and SDS-PAGE followed by colloidal gold staining. Dynamic light scattering was used to examine the size of the different OMVs both in the sterile culture medium following harvest as well as in the purified OMV samples. Cytotoxicity assays were performed with THP-1 cells differentiated to a macrophage-like phenotype with phorbol 12-myristate 13-acetate (PMA). Cytotoxicity was measured following overnight exposure and determined by assay of LDH release.

*Results*: The yield of OMVs using ultracentrifugation was low and associated with elevated ratios of protein to LOS content. Thus, OMVs isolated by SEC were used in functional assays. As assessed by both SEC and dynamic light scattering, we demonstrate that OMVs produced from cell cultures harvested during the late logarithmic phase of growth (8h) were larger in average radius than those produced from cell cultures harvested during late stationary phase of growth (18h). Additionally, after normalization for the LOS content in OMVs, the smaller OMVs produced from cells in late stationary phase growth induce greater cytotoxicity in THP-1 cells than those produced from cells in late logarithmic phase growth. Cytotoxicity was observed at concentrations of LOS as low as 2-10 ng/mL.

*Discussion and Future Directions:* Even when normalizing for LPS content, the smaller OMVs isolated at 18h culture induce greater cytotoxicity than those collected at 8h. This observation suggests that the context in which LPS is delivered to the host cells regulates the extent of noncanonical inflammasome activation. Our results also highlight the advantages of using radiolabeled bacteria, because it allows analysis of the quality and yield of OMV isolation. In future studies, we will use caspase 4/5 knockout THP-1 cells to determine the extent to which our observed cytotoxicity is due to the noncanonical inflammasome. We hypothesize that smaller OMVs deliver a greater quantity of activating LPS to the cytosol. Thus, future studies will also use subcellular fractionation of cells that have ingested OMVs to quantitatively determine the intracellular fate of OMV-derived LPS.

# Loss of RGS2 in the placenta: Consequence of reduced HDAC activity, and contributor to the pathogenesis of preeclampsia?

John W. "Jackson" Walsh, Katherine J. Perschbacher, Guorui Deng, and Justin L. Grobe Department of Pharmacology, University of Iowa Carver College of Medicine

Preeclampsia (PreE) is a hypertensive disorder of pregnancy which affects 3-5% of all pregnancies worldwide and kills approximately 76,000 mothers and 500,000 children each year. Preeclampsia presents with new-onset hypertension, proteinuria, and may progress to seizures or death. The underlying pathogenesis of PreE remains poorly understood, though it clearly involves a dysfunctional placenta; the only reliable therapeutic intervention is initiating labor of both child and placenta, which can lead to long-term health complications for both mother and child especially if preterm. Evidence supports altered/sensitized G protein signaling during PreE, and Regulator of G protein Signaling (RGS) proteins function as endogenous "brakes" on G protein signaling. Population studies from Norway have identified a single nucleotide polymorphism (rs4606) in the RGS2 gene as a risk factor for PreE. Our lab has determined that RGS2 mRNA levels are reduced in PreE placenta, regardless of rs4606 genotype. Further, we have demonstrated that selective disruption of RGS2 within the feto-placental unit in wildtype C57BL/6J dams is sufficient to induce hypertension, proteinuria, and selected molecular signatures of PreE within the placenta. As these findings support the novel concept that reduced placental expression of RGS2 represents a risk factor and mechanistic contributor to the pathogenesis of PreE, we sought to clarify the molecular mechanism of reduced placental RGS2 expression in placenta during PreE. RGS2 expression is stimulated in vascular smooth muscle by cAMP/CREB signaling, and therefore we hypothesized altered cAMP/CREB signaling in the PreE placenta. Deidentified PreE placenta, obtained from the University of Iowa Maternal-Fetal Tissue Bank exhibited increased levels of phosphorylated CREB, and in silico reanalyses of placental transcriptomes from a published dataset (NCBI GEO GSE75010) demonstrated significant enrichment for CREB target gene expression by Gene Set Enrichment Analysis. Therefore, CREB signaling is increased in PreE placenta. Forskolin-mediated stimulation of cAMP/CREB signaling in immortalized first-trimester human placental trophoblasts (HTR8/SVneo) resulted in increased CREB occupancy at the RGS2 promoter (by chromatin immunoprecipitation), and RGS2 expression (by qPCR), as expected. Therefore, CREB signaling should stimulate RGS2, yet RGS2 expression is decreased in PreE placenta. Interestingly, we discovered that the stimulation of RGS2 expression and the recruitment of CREB to the RGS2 promoter by forskolin was sensitive to the inhibition of pan-histone deacetylase activity (HDAC) by suberoylanilide hydroxamic acid (SAHA, or Vorinostat), but expression of RGS2 was not sensitive to the Class 1 and 2A HDAC inhibitor, UF010. Further, CREB occupancy at the RGS2 promoter, but not other CREB target genes (such as cFos), was inhibited by SAHA. This implies that HDAC class 2B (including HDAC6 or HDAC10) activities are required for the recruitment of CREB to the RGS2 promoter, and therefore cAMP-mediated stimulation of RGS2 expression. These findings (i) identify RGS2 as one of the subset of CREB target genes that require HDAC activity, such as CREM and NR4A3, (ii) specifically implicate the Class 2B subset of HDAC enzymes in this process, and (iii) demonstrate that suppressed HDAC Class 2B activity in the placenta may represent a novel risk factor or diagnostic for PreE, at least in part through the modulation of RGS2 expression.

## The influence of chronic cerebellar stimulation on cognitive function and circuitry

K. P. Walsh, BA, MS,<sup>1</sup> J. Heskje, BS,<sup>1</sup> P. W. Abbott, BS,<sup>1</sup> K. L. Parker, PhD<sup>1</sup> <sup>1</sup>Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, IA

**Introduction:** In neuropsychiatric diseases such as schizophrenia and autism, deficits in working memory, attention, reasoning, and timing are accompanied by cerebellar abnormalities – both structural and functional<sup>7–12</sup>. Yet, the mechanisms by which the cerebellum modulates the frontal cortex in pursuit of cognitive processing remain unknown<sup>1–3</sup>. Recent data have shown that optogenetic cerebellar stimulation at 2Hz can reinstate brain rhythms necessary for accurate performance on a time estimation task (in the seconds range) that relies on executive function and recruits the frontal cortex<sup>13</sup>. This is particularly relevant to patients with schizophrenia because cognitive deficits are reduced following cerebellar transcranial magnetic stimulation (TMS) in these patients<sup>14,15</sup>. Here we assess functional and structural changes that occur after two weeks of daily cerebellar stimulation by examining learning related changes on an interval timing task and histologic changes in structural plasticity. These results could help refine and improve existing treatment paradigms and inspire mainstream cerebellar-focused treatments for cognitive dysfunction.

**Objective:** To identify the mechanisms by which chronic cerebellar stimulation modulates frontal cortical activity.

**Methods:** Male Long Evans rats were infused bilaterally in the lateral cerebellar nucleus (LCN) with either AAV2-CamKII-mcherry-Channelrhodopsin (ChR2) or vehicle AAV lacking channelrhodopsin. All animals were then implanted bilaterally with optical cannulae targeting the ventrolateral thalamus. After recovery the rats were water restricted and trained to make operant lever presses to receive a water reward. After fixed ratio training, they anticipate rewards for responses occurring after a 12 sec temporal interval following the onset of a discriminative light stimulus. Rats received 2 weeks of daily 2 Hz cerebellar stimulation that began at the trial start and end after the 12 second interval has elapsed. Learning was analyzed by quantifying how efficiently animals time the interval. Rats were transcardially perfused with 1% then 4% formalin both with 0.125% gluteraldehyde. Brains were confirmed via fluorescence microscopy. Stereology was used to quantitatively analyze histological samples. A vibratome was used to collect 250  $\mu$ m-thick sagittal tissue sections from the frontal pole for fluorescent dye injections. Intracellular fluorescent dye filling was performed by iontophoretically injecting pyramidal neurons in MFC with the fluorescent dye Lucifer yellow. Reconstructed neurons, arborizations and spine morphometrics were compared between groups.

**Results:** Our preliminary analyses reveal inconsistent effects of 14 days of daily 2 Hz stimulation on timing accuracy as measured by the number of rewarded presses/total number of presses. Additional measures of timing performance will be calculated including the efficiency of responses around the time of reward availability and the curvature or the rate of responses that increases over the interval. Histological confirmation of injection site in the LCN, virus axonal transport, and optic cannula placement in the ventrolateral thalamus are still required. Analyses of are ongoing for changes in dendritic arborization and dendritic spine morphology of frontal cortical neurons following cerebellar stimulation.

**Conclusion:** We hypothesized that 2 weeks of daily 2Hz cerebellar stimulation would facilitate learning and timing accuracy or the rate of learning the interval timing task. This work is still in the preliminary stages and the results are currently inconclusive. As we continue collecting data for this project, we will examine the effect of stimulation of dendritic morphology and use diffusion tensor imaging to examine the integrity of the white matter tracts in both stimulated and sham animals. These data could provide insight into how cerebellar stimulation influences the frontal cortex and cognitive performance.

# Two-stage exchange arthroplasty for prosthetic joint infection: If at first you don't succeed, should you try again?

David L. Wang, MS, Timothy S. Brown, MD, Nicolas O. Noiseux, MD Jesse E. Otero, MD, PhD

Background: Patients who acquire infection of prosthetic hip and knee joints are particularly ill. Their comorbidities render them susceptible to infection, but also make fighting infection a challenge. Two-stage exchange arthroplasty is the gold standard for treatment of prosthetic joint infection. We sought to determine the fate of patients who undergo resection arthroplasty as a first stage in the process of twostage exchange. We then analyzed the demographic, laboratory, and health status determinants of their outcome.

Purpose/Aims:

- 1. What are the clinical outcomes following 2-stage exchange for chronically infected total hip and total knee arthroplasty?
- 2. What are the risk factors for failure of two-stage exchange for PJI?

Methods: With institutional review board approval, we queried our hospital database for all patients in the electronic medical record who underwent resection of a prosthetic hip or knee joint as the first stage of a planned two-stage revision protocol between 2009 and 2016. Surgeries were performed by 4 surgeons. We recorded patient age, sex, BMI, surgical history, infectious laboratory data, as well as health status variables including McPherson classification, Charlson comorbidity index, and smoking status. Primary outcome analyzed was failure of the two-stage exchange protocol defined as failure to undergo second stage reimplantation as well as known ongoing infection or repeat surgery for infection after the second stage. Next, we utilized multivariate regression analysis to determine risk factors for these outcomes.

Results: Of one hundred sixty patients identified who underwent resection of a prosthetic hip or knee in the interval queried, 89 had minimum 2-year follow-up (27 hips and 52 knees). Mean follow-up was 56.3 months. Average age of the population was 64 years (range 43-84 years); 50 were males (56.2%), and 39 (43.8%) were females. Average number of prior same-joint surgeries was 2.75. In this cohort of 89 patients, 61 patients (68.5%) went on to have a second-stage re-implantation, and 58.4% of those resected were cured at minimum 2-year follow up. Of the 28 who did not achieve the second stage, 6 had fusion, 3 had girdlestone, 1 had amputation, 3 died, and 15 retained their spacer. Of the patients who underwent second-stage re-implantation, success was achieved in 85.25%. Mortality rate in our cohort was 14.6%. Independent risk factors for failure in our cohort were ESR>25 (Adjusted odds ratio OR 8.6), McPherson extremity grade 3 (OR 3.3), multi-organism infection (OR 7.1), and having had a prior resection (OR 5.2). Insurance status did not predict outcome.

Conclusion: Patients who undergo resection for prosthetic joint infection often fail the two-stage exchange process. Inadequate debridement in the initial resection is a significant predictor for failure of subsequent two-stage. In cases where patients have multiple independent risk factors, more conservative treatments should be considered before initiating the two-stage exchange protocol.

## **Dissecting Downstream Effectors of Lefl in Primary Airway Stem Cells**

Qi Wang, Weam Shahin, Charles Yeaman, John Engelhardt

Understanding the mechanisms behind airway repair is important for the development of cell and gene therapies for the treatment of airway injuries in diseases such as cystic fibrosis or complications after lung transplant. In previous lineage tracing experiments, glandular myoepithelial cells (MECs) were identified as reserve stem cells capable of differentiating into 7 airway cell types and establish residency in the surface airway epithelium (SAE). Lef-1, a factor regulated by Wnt signaling, is thought to be central to lineage commitment, proliferation and rapid migration of MECs from glans to the SAE. In this study, we attempted to develop an in vitro migration assay which is sensitive to Lef-I overexpression and can be used for rapid screening of Lef-I effector genes identified in RNA-seq data.

Various MEC lines were prepared from Cre reporter mice that induce human Lef-1 overexpression and/or fluorescent label in MECs. Cells were induced with tamoxifen or treated with Tat-Cre then sorted for pure cell populations. Proper expression profiles were assessed using immunofluorescence. Migration assay was performed on 804G coated tissue culture plates using barriers specifically designed for this experiment. Cell migration was assessed using time laps microcopy and Metamorph software quantification. CRISPR guides were designed targeting selected Lef-I effector genes (Adamts2, RhoJ and Slit2) using a paired-KO design and evaluated using in vitro cleavage assay. Cas9 expressing MECs were made using Lenti viral vector expression Cas9.

Three repeats of migration assay comparing Lef-I KI and WT MECs were performed. No differences in rate of migration was observed using wound closure assay. In vitro cleavage assay showed that RhoJ and Slit2 guides are functional and Adamts2 guides do not cleave efficiently.

It is unknown whether MECs migrate first or differentiate into an intermediate cell types before migration to populate the SAE. Strong in vivo evidence and other prior in vitro observations suggest that Lef-I KI MECs or their progeny migrate faster than its WT counterpart. Future experiments using cells under different culture media and culturing conditions will be attempted. Combining a functional assessment assay and CRISPR gene editing approach, we hope to identify genes essential for the migration of MECs from submucosal glands to the surface airway epithelium, which can be useful for the development of cell or gene therapies. Development of Diabetic Zebrafish Model for Genetic Screening Yixi Wang PI: Colin Nichols, Washington University School of Medicine Department of Physiology and Cell Biology Mentor: Christopher Emfinger

#### Abstract

Neonatal diabetes is a rare subset of the disease diabetes and affects an estimated 1 in 250,000 births. As in other types of diabetes mellitus, the body is unable to effectively control blood glucose levels due to a faulty insulin response. The ATP-sensitive potassium ( $K_{ATP}$ ) channel is instrumental in insulin response, and gain of function mutations in its two subunits, kir6.2 and SUR1, are the primary cause of neonatal diabetes.

Previous studies have shown that the SUR1 subunit, which regulates channel sensitivity, can be targeted with the drug sulfonylurea as a form of treatment for the disease. However, required level of treatment and symptom severity of the studied cases can vary widely. This variation in expression of the mutations can be caused by many underlying factors, some of which may be mutations in other parts of the genome. A possible method to isolate these modifiers is a forward genetic screen.

To do so, we made an inducible neonatal diabetes model. We chose to use zebrafish as our model organism because of their similarities to humans and other practical advantages. We created a kir6.2 gain of function construct and established lines of fish that expressed the mutation. After testing, they have recapitulated several aspects of the disease in humans. In addition, a few assays essential for the screening process have been developed. With these tools, we will be able to identify individuals that deviate significantly in expression of the disease and genotype them to find candidate genes that modulate neonatal diabetes in humans as well. This will improve our understanding of the disease and inform future treatment.

#### Impact of Medical Scribe Experiences on Subsequent Medical Student Learning

Sanjeeva Weerasinghe, Kelly Skelly MD, Marcy Rosenbaum, PhD, and Jeanette Daly, RN, PhD

### Abstract

#### Background

Medical scribing is an activity often pursued by people applying for health professional training (medical school, PA school); it involves acting as a member of a healthcare team who transcribes patient encounters in electronic medical records. Studies find medical scribing improves the flow of patients in clinic and helps physician communicate more with patients (Yan et.al 2015, Hess et.al 2015). Clinical scribes had the opportunity to develop scribe-patient relationships, which mirrored that of the doctor-patient relationship. To date, no research has examined the potential effects of scribing on the learning of clinical skills.

#### Purpose

The purpose of this study is to investigate student perspectives on the possible educational effects of medical scribing on their preparation and development of future clinical skills.

#### Methods

After Medical Curriculum Assessment Umbrella IRB approval was obtained from the Office of Consultation and Research in Medical Education, all medical and physician assistant students at the University of Iowa Carver College of Medicine were contacted and asked to respond to a survey regarding medical scribing. In total 608 students were contacted 3 times to participate in the survey. On completion of the survey, each participant was asked if they were willing to further participate in a direct interview.

#### **Data Collection:**

Next, the students were interviewed about their experiences and how they valuable they felt their experiences to be when learning clinical skills. Some specific questions include: What impact do you feel scribing has had on your learning about medical interviewing/history taking? How has it impacted clinical note writing? Do you feel scribing has had impact on your overall medical knowledge? We will be recording their answers during each session. Then we transcribed each of their answers and try to note if any patterns in answers appears.

#### Data Analysis

Interviews with students were transcribed verbatim. Descriptive statistics were conducted for each survey question. Confidence-Likert scale results were converted to dichotomous variables. Chi-square tests were conducting comparing scribes and non-scribes differences on confidence in note writings, medical history taking, year in medical school, and gender via SPSS-version 24. Thematic coding and analysis of interview transcripts and open-ended survey responses were conducted using Nvivo qualitative analysis of software.

#### Results

With a response rate of 214/608 students, 66 students were scribes. We interviewed 18 students. Both the quantitative survey and the interview analysis found a significant difference in confidence scores in regards to note writing between scribes and non-scribes. We did not find any significance confidence in history taking between scribes and non-scribes. Thematic analysis consistently identified ways that scribing impacted their subsequent learning in the areas of note writing, history taking and communication, Exposure to healthcare environment, and Team dynamics.

#### Conclusions

Findings from the study suggest that the scribing experience impacts confidence and perceived skill in clinical note writing in our students who scribed prior to medical/PA school. Additionally, scribing enabled students to observe history taking and clinician patient communication and may enhance learning of these skills. Moreover, scribing provides the exposure to the healthcare environment familiarizes learners with the medical environment, clinician work life and healthcare teams. The prevalence of scribing amongst learners in our study may not be representative of all health professional students. The positive or negative impact of scribing experience on clinical skills was not objectively measured. Future research could explore both the prevalence of scribing experience nationally and the actual impact on clinical skill development through systematic comparative observations of scribes vs non-scribes.

The Utility of Routine X-ray Imaging Following Chest Tube Removal Student: Benjamin Wilkinson, M2 Mentor: Kalpaj R. Parekh, MBBS

**Introduction/Background:** Following lung resections, the use of tube thoracostomy is routinely employed to keep the lung inflated. The standard of care for management of chest tubes is to obtain a routine chest X-ray immediately following tube removal to evaluate for complications. Post removal management may be better guided by clinical information such as the patient's symptoms after tube removal reducing the need for imaging, radiation exposure, and the cost of delivering healthcare.

**Hypothesis:** Our central hypothesis is that routine post chest tube pull chest X-ray is not necessary in lung resection patients, and that clinical symptoms will have a stronger association with significant complications than routine X-ray findings.

**Methods:** After approval from Institutional IRB, retrospective chart review of patients that underwent pulmonary resection between July 2014 and October 2017 at the University of Iowa was conducted. The primary outcome was defined as complications requiring chest tube reinsertion within 30 days. A secondary outcome was defined as "any complications" including chest tube reinsertion, readmission, ED visit, or the development of a new pneumothorax or pleural effusion within 30 days.

**Results:** During the study period 100 subjects underwent lung resections. Of these 56 had no immediate chest X-ray after tube pull and 44 had one. Median age was 65 years in both groups. Two patients required chest tube reinsertion within 30 days (one in each cohort) and 4 patients required readmission within 30 days (2 in each cohort). All 6 subjects that had post removal symptoms developed complications. Within 30 days 1 required readmission, 4 visited the ED, and 1 required chest tube reinsertion. None the 94 patients without symptoms required readmission or ED visits, and only 1 had a chest tube reinsertion.

**Discussion:** The data shows no significant difference in outcomes between groups with or without X-ray. There was also no evidence for a relationship between X-ray findings (normal vs. abnormal) and either outcome. There is a statistically significant relationship between clinical symptoms and any complications (p value 0.0024, Fisher's exact test, Holm-Sidak adjusted). These findings support our hypothesis that routine post pull X-ray is unnecessary and that clinical symptoms can guide treatment.

			Р
Variable	No X-ray	X-ray	Value
n=	56	44	
Male	32	20	
Female	24	24	
Thoracotomy	30	12	
VATS	20	25	
Conversion	6	7	
Lobectomy	53	41	
Wedge Resection	3	3	
Left side	25	25	
Right side	31	19	
Any Complication	12	17	0.329
Readmission within 30			
days	1	0	
ED visit within 30 days	2	2	
Reinsertion of Chest Tube	1	1	0.9999

**Table 1.** Retrospective chart review of 100 pulmonaryresection patients.

### Exposure to Fluid Shear Stress Results in Activation of YAP/TAZ in prostate cancer cells Sophia Williams-Perez, BA<sup>1</sup>, Devon Moose, MS<sup>12</sup>, Michael Henry, PhD<sup>12,3</sup>

<sup>1</sup>University of Iowa Carver College of Medicine, <sup>2</sup>Department of Molecular Physiology and Biophysics, <sup>3</sup>Holden Comprehensive Cancer Center, University of Iowa, 52242, USA

BACKGROUND: Prostate cancer is the second-leading cause of cancer-related deaths in the country. Metastasis, the spread of cancer to vital organs, is responsible for the lethal consequences of prostate cancer. It is known that in order for metastasis to occur, tumor cells must leave the primary tumor, enter circulation, lodge in distal microvasculature, exit circulation, and then proliferate. Paramount to understanding how metastatic cancer manifests is the role of circulating tumor cells (CTCs). CTCs are cancer cells that have escaped the primary tumor site and enter systemic circulation, a fluid microenvironment distinct from the primary tumor. In this fluid microenvironment, CTCs are exposed to hemodynamic forces such as fluid shear stress (FSS). It has been commonly thought that hemodynamic stresses readily destroy the majority of CTCs. However, recent research has elucidated that transformed prostate epithelial cells are in fact more resistant to FSS than their non-transformed counterparts. Moreover, we have recently shown that exposure to FSS activates Rho GTPases, which could have effects not only on the ability of cancer cells to withstand FSS, but also on downstream events in metastasis such as extravasation or survival at distant sites.

HYPOTHESIS: Exposure to fluid shear stress results in an adaptive resistance through small GTPases that control cellular contractility and leads to YAP/TAZ activation.

METHODS: To analyze RhoC and Rac1 activity in sheared versus non-sheared cells, PC-3 prostate cancer cells were used in a GST fusion protein pull-down assay. PC-3 cells were divided into sheared and non-sheared populations. Sheared PC-3 cells were subjected to two pulses of FSS at 250 µL/sec. Both sheared and non-sheared cells were incubated with GST-RBD to pull-down RhoC or with GST-PBD to pull-down Rac1. Results were attained via gel electrophoresis followed by visualization using western blot methodology. To determine the activation of YAP/TAZ in sheared versus non-sheared cells, PC-3 cells were analyzed via western blot to assess YAP/TAZ and phospho-YAP protein level expression. In addition to PC-3 cells expressing endogenous RhoA, PC-3 cells with knocked down RhoA were used to further assess the association of RhoA activity on downstream YAP activation. Sheared cells were subjected to ten pulses of FSS at 250 µL/sec and samples were collected immediately after shearing, 1 hour, 3 hours, and 6 hours after shearing to evaluate time-dependence of YAP/TAZ protein expression.

RESULTS: Western blotting confirmed a difference in activated protein expression for RhoC and Rac1 between the sheared and non-sheared PC-3 cell populations. For RhoC, there was more activated protein expression at 2 pulses of FSS than at 0 pulses whereas for Rac1, there was more protein expression at 0 pulses than at 2 pulses of FSS. For YAP and phospho-YAP, western blot confirmed a difference in phospho-YAP but no difference for total YAP in PC-3 cells. There was greater phospho-YAP expression in unsheared samples than sheared. In RhoA knockdown PC-3 cells the results were inconclusive.

CONCLUSIONS: When PC-3 cells were exposed to fluid shear stress, the activity of RhoC increased supporting the hypothesis that FSS exposure induces activation of small GTPases that aid in resisting FSS. The results also indicated that an increase in RhoC activity was correlated with a decrease in Rac1 activity, upholding a phenomenon that has been reported in literature. Additionally, expression of phospho-YAP was increased in unsheared PC-3 cells, supporting that FSS stimulates the activation of proteins within the Hippo signaling growth pathway. Moving forward, we plan to investigate the cellular localization of YAP/TAZ in PC-3 cells using fluorescence microscopy. Additionally, we will explore the long-term effects of FSS exposure adaptations on metastatic potential using a tail-vein model of metastasis and invasion using Matrigel and trans-endothelial migration assays.

## Electrocardiographic changes pre and post Transcatheter Pulmonary Valve Replacement

Beth Wole, BS<sup>1</sup>, Seth Garton, MS<sup>2</sup>, Jennifer Maldonado, BS, RTR<sup>2</sup>, Ian Law, MD<sup>2</sup>, Manish Bansal, MD<sup>2</sup>

Department of Pediatrics, Division of Cardiology, University of Iowa Carver College of Medicine <sup>1</sup>, University of Iowa Stead Family Children's Hospital <sup>2</sup>

**Background:** Transcatheter pulmonary valve replacement (TPVR) is a minimally invasive alternate to surgery for patients with right ventricular outflow tract (RVOT) obstruction and/or insufficiency resulting from various congenital heart defects. QRS duration has been shown to be associated with RV size in patients with pulmonary insufficiency. In this study, we evaluated changes in EKG and Holter studies pre- and post TPVR.

**Methods:** A single center retrospective chart review was conducted on patients who underwent TPVR from 2011 to 2018 for pulmonary valve stenosis (PS) and/or insufficiency (PI). Patients with previous PVR and varying types of RVOT (native annulus, trans-annular patch, bioprosthetic valves and conduits) were included in the study. Data collected included prior cardiac surgeries, arrhythmia history and pre- and post TPVR EKG and Holter studies.

**Results:** A total of 50 patients (56% male, n=28) underwent TPVR during the study period, all of which had pre and post EKG data available for analysis. At time of the procedure, median age was 17.36 years (range: 4.74-62.04); median height was 159.5cm (range: 107.5cm-196cm), and mean weight was 59.48 kg (sd= 23.25 kg). Prior to TPVR, 46% had a valved conduit (n=23), 24% had a bio-prosthetic valve (n=2 placed in conduit, n= 10 placed in RVOT) and 30% had a native annulus (n=1 post valvuloplasty only, n=14 post trans-annular patch). Indication for TPVR was combined PI and PS (n = 29), isolated PI (n = 13) and isolated PS (n = 8). 70% of the patients received a Melody valve implantation, while 30% of the patients had a Sapien valve.

Examination of pre- and post TPVR EKGs showed no statistically significant changes in QRS duration (pre = 130.3 ms vs post = 131.7ms), p = 0.53). However, there was a significant decrease in heart rate (pre = 74.1 vs post = 68.82, p = 0.0018). Three of the patients (6%) had newly developed ventricular tachycardia (VT) on Holter studies post-procedure. These three patients all had native RVOT. Review of additional Holters on these patients showed a resolution of VT in two of the patients.

**Conclusion:** The changes in QRS duration post TPVR were not statistically significant. However, there was a significant decrease in heart rate following TPVR. Early ventricular arrhythmias were infrequent and most resolved at follow-up.

## Morning Blood Pressure Surge is Blunted in Individuals with Chronic Anxiety: Relation with Nocturnal Blood Pressure Dipping

Student: Nealy A. Wooldridge, M1 Mentor: Gary L. Pierce, PhD Collaborators: Rachel E. Luehrs, Seth W. Holwerda, Jess G. Fiedorowicz

**Background.** Anxiety disorders are the most common mental health problem in the United States, occurring in about 18% of adults per year and is an established risk factor for cardiovascular disease (CVD). A meta-analysis demonstrated that having an anxiety diagnosis increased the risk of having CVD by 26% and cardiac mortality by 48%. However, the mechanisms by which anxiety contributes to an increased CVD risk are not well understood. An exaggerated morning blood pressure (BP) surge (MBPS) is associated with an increased risk of cardiovascular and cerebrovascular events and all-cause mortality. However, it is unclear whether chronic anxiety alone is associated with an exaggerated MBPS because results from previous studies examining this relation have varied depending on the study population, assessment of anxiety, and definition used to calculate MBPS. Identifying a link between chronic anxiety and MBPS would have major clinical implications and may lead to the discovery of therapeutic targets to reduce the heightened CVD risk observed in individuals with chronic anxiety. Therefore, the aim of this study was to determine the extent to which individuals with chronic anxiety, who are otherwise healthy, display an exaggerated MBPS compared with individuals without chronic anxiety. We hypothesized that MBPS is greater in individuals with chronic anxiety.

Methods. A total of 81 participants with and without chronic moderate to severe anxiety that were otherwise healthy were studied (age:  $37 \pm 12$  years; 53 females, 28 males; 47 with anxiety, 34 controls without anxiety). Generalized Anxiety Disorder 7-item (GAD-7), a self-report scale was used initially for pre-screening and in part for grouping individuals into the anxiety or control groups. Anxiety was also assessed using the State-Trait Anxiety Inventory (STAI), a self-report survey that assesses "state" anxiety that reflects how the subject feels for two weeks prior and at the time the survey is taken, and "trait" anxiety that reflects a long-term tendency to be anxious. A secondary assessment of anxiety symptoms was the Beck Anxiety Inventory (BAI). Noninvasive 24-hour ambulatory BP was obtained using oscillometric monitors (model 90207, SpaceLabs Inc.) and all subjects kept a written record of their activities and sleep period for the 24-hour monitoring period. MBPS was assessed in three ways: (1) Sleep-Trough Surge - average of three readings centered on the lowest night BP (night reading) and average of readings for two hours after waking (morning reading); (2) Pre-waking Surge - average of two hours prior to waking up (night reading) and average of two hours after waking (morning value); (3) Lowest Average Sleep-Trough Surge - lowest average of two consecutive readings during the night (night reading) and average of readings for two hours after waking (morning reading). For all definitions, MBPS was calculated as the morning value minus the night value. Systolic nocturnal dipping percentage was calculated with the following equation: [1 - (Evening Systolic BP/Daytime Systolic BP)] x 100, utilizing 24-hour averages of evening and daytime systolic blood pressure. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI).

**Results.** Lowest average sleep-trough MBPS was significantly lower in individuals with moderate to severe anxiety compared with individuals without anxiety, as measured by the GAD-7 (P = 0.01). Anxiety scores were significantly correlated with lowest average sleep-trough MBPS for STAI (state anxiety: r = -0.24, P = 0.03; trait anxiety: r = -0.23, P = 0.04), and was near significance using BAI (r = -0.20, P = 0.07). Additionally, systolic nocturnal BP dipping was significantly associated with MBPS (r= 0.64, P < 0.001) in the whole cohort and was lower in individuals with anxiety (P = 0.04). These results were similar for the pre-waking and sleep-trough MBPS definitions. Interestingly, although individuals with anxiety had significantly worse reported sleep quality via PSQI (P < 0.001), PSQI score was not associated with MBPS or systolic nocturnal dipping (r = -0.23, P = 0.10; r = -0.13, P = 0.35; respectively). Aforementioned results remained significant after controlling for age, sex, and body mass index (P < 0.05).

**Discussion.** In contrast to our hypothesis, MBPS appears to be blunted in individuals with chronic anxiety, compared with non-anxiety controls and MBPS (using any definition: sleep-trough, pre-waking, lowest-average sleep-trough surge) was not positively associated with any of our measures of anxiety (STAI, GAD-7, BAI). Systolic nocturnal BP dipping was also significantly blunted in individuals with anxiety, suggesting that the attenuated MBPS observed in adults with anxiety is a result of blood pressure not decreasing appropriately at night. Additionally, subjective sleep quality was significantly worse in individuals with anxiety but was not related to systolic nocturnal dipping or MBPS. Further studies are needed to determine the clinical significance for the blunting of MBPS and attenuated nocturnal BP dipping in individuals with anxiety.

## The Effect of Visual Aids in Preoperative Patient Counseling for Oculoplastic Surgery

Kelly H. Yom, BA<sup>1</sup> Erin M. Shriver, MD, FACS<sup>2</sup> Kenten D. Kingsbury, CNA<sup>3</sup> Keith D. Carter, MD, FACS<sup>2</sup> Audrey C. Ko, MD<sup>2</sup>

<sup>1</sup> Carver College of Medicine, University of Iowa, 200 Hawkins Drive, Iowa City, IA, 52242, USA
<sup>2</sup> Department of Ophthalmology and Visual Sciences, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA, 52242, USA
<sup>3</sup> University of Iowa, 200 Hawkins Drive, Iowa City, IA, 52242, USA

**Background:** In preoperative patient counseling, the effect of exemplary immediate postoperative photographs demonstrating common events such as bruising, swelling, and asymmetry has not been previously evaluated.

**Purpose:** This study investigates the effect of such visual supplementation with exemplary immediate postoperative photographs on patient education regarding the healing process after oculoplastic surgery. This study also determines if there are significant differences if counseling is performed by the medical team in person versus prerecorded video.

**Methods:** A prospective randomized controlled trial was conducted in compliance with the Institutional Review Board. Consecutive surgical patients seeking oculoplastic eyelid surgery at a single institution were randomized to an "oral only" or "oral and visual" patient education group. The "oral only" group received routine preoperative oral counseling regarding what to expect after the operation. The "oral and visual" group received routine oral counseling supplemented with exemplary photographs demonstrating common postoperative findings – such as swelling, bruising, and asymmetry – either via the medical team in person or prerecorded video. Patient-reported emotions and expectations of postoperative findings were assessed by validated survey instruments (the State-Trait Anxiety Inventory and Surgical Fear Questionnaire). Postoperative surveys assessing the same parameters were administered during routine follow up visits at postoperative week one and month two.

**Results:** 59 patients were included. 19 received oral only education, 18 received oral education accompanied by photographs, and 22 received oral education via video. No significant differences were noted in patient demographics between groups (Table 1). Preoperatively, there were no significant differences in patient-reported feelings of fear, anxiety, or preparedness (Table 2). There were also no significant differences in patients' expectations of post-operative adverse events (Table 2). At the one week postoperative visit, there were no significant differences in patient feelings of anxiety, preparedness, or satisfaction, nor were there significant differences in patient-reported adverse events (Table 3). The triage call rate was also similar amongst all three groups (Table 3).

**Conclusion:** Visual supplementation during patient counseling does not significantly impact triage call rates or patient expectations, anxiety, or satisfaction regarding their surgery and postoperative healing process compared to standard oral counseling alone. Moreover, patient education via video is equivalent to counseling in person by the medical team. Thus, implementation of video counseling may help to standardize the education given to patients and increase efficiency without affecting the patient experience.

Qualitative Systematic Review of Reports of Dural Puncture and Cerebral Vein Thrombosis. Grant Young, Paloma Toledo, Cynthia Wong

**Introduction:** Cerebral venous thrombosis (CVT) is one of the most common causes of ischemic events during pregnancy. When diagnosed and treated early, CVT usually has a favorable outcome. Women often received a neuraxial (spinal or epidural) anesthesia in the peripartum period; dural puncture may be intentional or unintentional is associated with a risk of postdural-puncture headache (PDPH). CVT after dural puncture has been reported, but it is unclear whether there is a causal relationship between dural puncture (usually in the context of neuraxial analgesia/anesthesia) and CVT. The goal of this qualitative systematic review is to review the literature for all reports of CVT in the postpartum period, and identify patient and procedural characteristics, and patterns that might explain a relationship between PDPH and CVT.

**Methods:** A systematic search of all published cases of CVT during pregnancy was conducted in May 2018 using PubMed and EMBASE. Inclusion criteria included cases of CVT in the postpartum period in which case characteristics were reported. Cases were excluded if there was no discussion of CVT, the CVT was antepartum, or the CVT occurred in the fetus or newborn. Non-English language, nonhuman animal studies, and conference abstracts were excluded. All titles and abstracts were reviewed by one author (GY) and a full text review was conducted on the remaining articles. A standardized data form was used to abstract case details.

**Results:** Sixty-nine articles were included; 101 cases of CVT were identified. Cases were divided into two categories: neuraxial anesthesia attempted/performed and no neuraxial anesthesia described or attempted/performed. In the first group (n=56), the mean age was 26 y with 21 cases of full-term birth. Thirteen patients had conditions of increased hypercoagulability (heterozygous Factor V Leiden mutation and protein S deficiency). Fifty-four cases reported headache, 41 were positional. Other common symptoms were weakness and seizures. Thirty-three patients made a full recovery and no deaths were reported. In the second, non-neuraxial group (n=45), the mean age was 26 y. Twenty-one patients had hypercoagulable conditions (protein C and S deficiency, hyperhomocysteinemia, cystathionine-beta-synthase deficiency, and hyperfibrinogenemia). Forty cases reported headache; only one was positional. Twenty-nine patients made a full recovery and one death was reported.

**Discussion and Conclusion:** This qualitative systematic review demonstrates the heterogeneous course of postpartum CVT. Overall, 94 of 101 cases reported a headache but the neuraxial anesthesia group more often included a positional component to the headache, typical of a PDPH. The positional aspect can make diagnosis difficult due to the similar presentation of PDPH. It is also possible two different pathologic processes contributed to the headache. Some authors hypothesized that dural puncture may contributed to the risk of CVT by altering intracranial pressure/flow relationship, and the risk may be exacerbated in women with baseline hypercoagulation (over that normally associated with pregnancy and the postpartum period). This review of CVT in obstetric patients represents a complete collection of cases in the published English literature. Further study of cerebral venous thrombosis is necessary to better define the correlations, if any, between dural punctures and occurrence of CVT.

# Epigenetics of Delirium: Investigating DNA Methylation Changes in the Tumor Necrosis Factor alpha Gene in Search for a Delirium Biomarker

Tong Yu, M2, Benjamin Hing, PhD Gen Shinozaki, M.D. Department of Psychiatry, University of Iowa

**Background**: Delirium is a state of acute confusion characterized by impaired attention and cognition. It is commonly seen in elderly patients at the hospital, and these patients have increased rates of mortality and are highly susceptible to injuries such as falls, which leads to longer hospital stays and higher medical bills. Delirium is currently underdiagnosed and undertreated, and the pathogenesis is not well defined. Patients with delirium who underwent surgery have been shown to have higher levels of serum cytokines, and rat models of delirium have shown similar results, with increased level of proinflammatory cytokines such as *IL-1 beta*, *IL-6*, and *TNF-alpha*. The animal model also showed enhanced inflammatory response through microglia, which suggests a potential pathogenesis for delirium where aging may lead to epigenetic changes in certain proinflammatory cytokine genes specifically in microglia ('microglia priming') that leads to enhancing their expression upon exogenous insults. This may contribute to the development of delirium-like cognitive disturbances. Thus, epigenetic changes in the cytokine gene *TNF-alpha* in human could serve as a potential biomarker for delirium.

**Hypothesis**: DNA methylation level in pro-inflammatory cytokine gene *TNF-alpha* is lower in blood samples of elderly inpatients with delirium compared to control.

**Method**: We recruited delirium patients admitted to UIHC and age and gender matched controls of non-delirious patients. Blood samples were collected from a total of 57 subjects (average age 69.0 yo). DNA was isolated using Illumina MasterPure DNA extraction kit and deaminated with EZ DNA Methylation Kit (Zyme Research) prior to investigating DNA methylation (DNAm). First, we used the Illumina EPIC array, which targets ~850,000 CpG sites across the genome, to evaluate differences in DNAm level between 13 delirium cases versus 13 controls. Specifically, we tested the correlation between DNAm and age among CpGs in the *TNF-alpha* gene listed on the EPIC array. Next, additional blood samples were analyzed from 16 patients with delirium and 15 patients without delirium by bisulfite-pyrosequencing at the same CpGs in the *TNF-alpha* gene. The CpGs were further grouped into Differentially Methylated Regions (DMRs). One-way ANOVA in Prism was performed to compare DNAm differences of the DMRs between delirious and control groups.

**Result**: For the EPIC array data, 24 CpG sites in the TNF-alpha genes were evaluated which showed negative correlation between age and DNAm in delirium cases. Four CpGs in particular had significant negative correlations (Figure). In contrast, the control group had a mix of both positive and negative correlation. For the second cohort of 31 subjects, there was no significant differences in DNAm at the DMRs of the *TNF-alpha* gene between delirious and control groups

**Conclusion:** The greater number of CpGs being negatively correlated between age and DNAm suggest increased *TNF-alpha* levels in delirious patients. This is consistent with the involvement of pro inflammation in mediating delirium. The lack of significant differences in DNAm between delirious and control groups suggests a larger cohort may be required to provide greater statistical power to identify those differences. In addition, other relevant pro-inflammatory cytokine genes, such as *IL1-beta and IL6* were not tested, which warrant further investigation.



Figure: Distinct correlation patterns of age and blood DNAm at 4 CpGs in the TNFalpha gene between delirium cases (red) vs nondelirium controls (blue). Red indicates cases and blue indicates controls. Delirium group showed DNAm decrease along with age, whereas controls showed DNAm increase with age, showing distinct patterns of correlations. 4 CpGs were all statistically significant at alpha=0.05

#### New Insights into Data-Driven Biomarkers, Mechanisms, and Treatments of Delirium

Kasra Zarei<sup>1,2</sup>, MS; Aaron Boes<sup>1,2</sup>, MD, PhD; Gen Shinozaki<sup>1,2</sup>, MD, MS

<sup>1</sup>Medical Scientist Training Program, Carver College of Medicine; <sup>2</sup>Department of Psychiatry, Carver College of Medicine

#### Background

Delirium is a term of many meanings, characterized by an acute, disturbed state of mind. Many subtypes are observed in a general hospital whether following sepsis, surgery, anesthesia, or procedures including electro-convulsion therapy. Delirium is a prevalent and dangerous state of confusion that affects millions over 65 years of age. A lack of effective screening methods in high-volume hospital settings results in delirium being seriously underdiagnosed and undertreated. Undetected delirium in hospitalized elderly patients greatly increases mortality, length of stay, and rates of post-discharge institutionalization. One-year mortality rates after delirium can be as high as they are for heart attacks. Beyond those human health costs, annual financial losses due to delirium are estimated to be over \$150 billion in the U.S. alone. Delirium requires treating the underlying etiology and restoring the patient's consciousness. Regarding the latter, there is considerable room for methodological improvement, which requires a robust method to diagnose and monitor delirium. Current diagnostic and screening methods for delirium are based on various, subjective questionnaires that have a number of drawbacks.

#### Purpose

The purpose of this work was to develop an objective biomarker of delirium in humans and rodents using frontal electroencephalography (EEG). An understanding of frontal EEG changes could guide the development of datadriven interventions to treat delirium.

#### Methods

Resting-state frontal EEG recordings were collected in 274 subjects (control and inpatients who were diagnosed with delirium). In an additional 38 subjects undergoing electroconvulsive therapy (ECT), resting-state frontal EEG recordings were collected at baseline and immediately following ECT (during the post-ictal confusion state). EEG recordings were also obtained in a mouse model of delirium induced following intraperitoneal injection of lipopolysaccharide (LPS).

#### Results

We established a novel measure of delirium derived from frontal EEG, defined as a frequency specific ratio comparing low frequency (delta/theta) to high frequency (alpha) EEG activity. This measure was significant in predicting changes between normal and baseline frontal EEG activity compared to frontal EEG activity during different sub-types of delirium. Interestingly, similar EEG changes were observed in a rodent model of delirium for the first time. Using our novel EEG findings in delirium, we were able to design and pilot multiple non-invasive neuromodulatory protocols using transcranial magnetic stimulation (TMS) and transcranial alternating current stimulation (tACS) that can treat delirium in any setting.

#### Conclusion

This work allows low-cost, rapid objective screening and quantification of delirium in unprecedented detail, and allows testing of translatable treatments in mice and humans, whether pharmacotherapy or personalized neuromodulation.