# Abstracts

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# Predicting Urine Drug Screen False-Positives Using Machine Learning

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**Introduction:** Immunoassay-based urine drug screens are commonly used to detect drugs of abuse in healthcare and legal settings. While these immunoassays offer relatively quick results, they are subject to false-positives due to cross-reactivity with non-target analytes. To date, efforts to identify cross-reactive compounds previously unreported by manufacturers of these immunoassays have relied on case reports and mining electronic health record data.

**Purpose:** We aimed to establish a novel approach to false-positive discovery by generating machine learning models for urine drug screen immunoassays that target amphetamines, benzodiazepines, or opiates. We then aimed to assess the effectiveness of these models in predicting known cross-reactive compounds as a proof-of-concept for future machine learning development as well as to identify compounds of interest for experimental testing.

**Methods:** Manufacturer package insert cross-reactivity data were used to develop machine learning models. Each model was validated using a nested 5-fold cross validation which randomly stratified a 20% hold out test set while using the other 80% as training data. With these models, pipelines using 10 different machine learning algorithms were used to generate prediction scores for compounds of a library we generated. Algorithms were assessed using the following statistical parameters: specificity, recall, precision, F-1-Score, accuracy, receiver operating characteristic, Cohen's Kappa, and Matthew's correlation. Lastly, we cross-referenced compounds with high prediction scores to published literature that reported compound cross-reactivity not included in manufacturer package insert data.

**Results:** The machine learning models produced for benzodiazepine assays statistically performed very well by all parameters, while models for opiates performed not as well but still acceptable. The worst performing models were those built for amphetamines, although most algorithms were acceptable. Several compounds were identified to have high prediction scores with compounds reported in the literature as cross-reactive. Exemplifying this process is the antiviral efavirenz, a drug whose cross-reactivity was not reported in package inserts. Efavirenz had high predictive scores across several algorithms for benzodiazepine assays and has been reported in the literature to produce false positives with certain benzodiazepine assays.

**Discussion and Conclusions**
The models produced in this study were generally statistically reliable, and numerous compounds predicted to be cross-reactive were supported by published literature. This innovative approach affords us the opportunity to refine models over time as new cross-reactivity data becomes available. We believe this study stands as a proof-of-concept that machine learning models built using cross-reactivity data can predict false-positives and therefore be a novel tool in false-positive discovery for immunoassays.

# Cemented vs. Cementless Total Knee Arthroplasty and Associated Learning Curve

Mentee: Trevor Allen
Mentor(s): Nicolas Noiseux MD, Taylor Den Hartog MD

Background:

Traditionally, total knee arthroplasty (TKA) has been performed utilizing cemented knee implants. While cemented TKA has an excellent track record, younger patients may benefit from bony ingrowth utilizing cementless implants. Successful bony ingrowth reduces the potential for long term aseptic loosening.
Cementless implants have shown similar short-term results as cemented TKAs in fields of pain relief, blood, loss, operation time, and corrective alignment. The ideal fixation method for TKA procedures is still debated as cemented vs. non-cemented techniques. Cemented TKAs have previously shown evidence of reduced loosening related to micromotion compared to those of press-fit implant. Other literature has previously associated poorer clinical outcomes and survival rate (99% cemented vs. 97% cementless) attributed to the use of press-fit components. Many of the poor outcomes attributed to cementless TKA are of unknown origin and justify further investigation.

Purpose:

To investigate the complications, failures, reoperations, and patient reported outcomes of the first 100 press-fit total knees performed by two fellowship trained Hip & Knee arthroplasty surgeons at UIHC and determine if a learning curve exists and how many cases it represents, for physicians transitioning to the use of cementless implants.
*Hypothesis:* Conversion from all cemented TKAs to some/many cementless TKAs is associated with a short learning curve period (less than 10-20 cases) in which physicians require longer operating times, may have more complications, but have no difference in PROs.

Method:

Retrospective chart review of the first 100 press-fit TKAs performed by 2 surgeons at UIHC. Cases will all be analyzed for complications, reoperations, failures, and patient-related outcomes. Complications and PROs will be evaluated for the first 50 cases versus the second 50 cases to evaluate for a “learning curve.” Analysis of the one-year post-operative radiographs of all these patients, for complications, signs of failure or loosening.

Results:
Conclusion/Discussion:
The project is ongoing and at this time a well-founded conclusion cannot be determined.

**Relationships between Lung Inflammation, Measures of Cognition, and Brain MRI in Heavy Smokers**

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*Background*: Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity, disability, and mortality in the world. Cognitive impairment has been increasingly recognized as a complication of COPD, but the underlying physiology impacting cognition is not fully understood. COPD is characterized by chronic lung inflammation, which can be quantified using measures from lung CT and Diffusion capacity of the Lungs for Carbon Monoxide (DLCO). A new lung CT quantification method, texture analysis, can identify inflammatory COPD phenotypes that may place patients at risk for changes in the brain.

*Aims*: The primary goal of the project was to perform texture analysis on lung CT scans from heavy smokers with and without COPD, and cross-sectionally examine associations between "bronchovascular associated pathology" (BVAP), Ground Glass Inflammation, and DLCO with findings from cognitive testing and brain MRI. We hypothesized that lung inflammation (i.e., increased BVAP and ground glass inflammation from texture analysis and decreased DLCO) would be associated with worse performance on cognitive measures of executive function and processing speed and decreased cerebral white matter structural integrity (fractional anisotropy [FA] from diffusion weighted imaging [DWI]).

*Methods*: Data from 82 heavy smokers (≥ 10 pack year history) participating in an on-going NIH funded study "*COPD and the Brain*" were analyzed. Post-Bronchodilator spirometry was administered to classify COPD status and severity of airflow limitation. Neuropsychological assessments measured executive functioning, processing speed, visuospatial skills, and language expressed as age-adjusted t-scores. The primary brain MRI outcome measure was cerebral FA from DWI. Texture analysis was performed using Adaptive Multiple Feature Method software to classify ground glass, BVAP, and normal lung. Measures were expressed as the percent of each lung classified as each texture. Generalized linear models were created to examine the association between BVAP, Ground Glass Inflammation, and DLCO with our primary outcomes (executive function, processing speed and FA). Age, sex, education, smoking exposure (pack-years), and current smoking status were included as co-variates in all models conducted using R software.

*Results*: Unadjusted analysis revealed significant ($p < 0.05$) associations between DLCO and visuospatial and language performance (visuospatial coefficient = 0.11768 [95% CI 0.03573621, 0.1996225], and language coefficient = 0.12570 [95% CI 0.02381895, 0.2275824]). After adjusting for co-variates, DLCO remained significantly associated with visuospatial skills (adjusted visuospatial coefficient = 0.12038 [ 95% CI 0.02567975, 0.21508007]). No significant associations were observed between DLCO and other outcomes, nor between texture analysis measures and all outcomes.

*Conclusions*: The current study is one of the first to examine the potential association between COPD phenotypes and brain outcomes using lung CT. While we observed an association between DLCO and some aspects of cognitive performance, lung inflammation assessed via texture analysis of lung CT data was not associated with our outcomes. Future research can build upon this analysis by including a larger sample size, including patients with more advanced COPD, and examining other COPD phenotypes identified using lung CT.

**Abstract**

**Title**: Experience of peripartum complications including puerperal infections, preeclampsia, and hemorrhage is independently associated with lower breastfeeding rates among first-time birthing parents

**Student**: Emily Anderson, M4

**Mentor:** Stephanie Radke, Obstetrics & Gynecology

**Background:** Complications during the pregnancy course are common, but little is known if certain complications affect one's ability to breastfeed exclusively.

**Materials & Methods:** This is a retrospective cohort study that looked at breastfeeding rates at three separate time points at a single tertiary center for 1,755 breastfeeding parents during July 1st 2016 through June 30th 2019. Complications such as obstetric hemorrhage, pre-eclampsia, infectious complications of pregnancy, obstetric anal sphincter injury, acute posthemorrhagic anemia, and diabetes and their association with breastfeeding rates were found using multinominal regression modeling and were adjusted for sociodemographic characteristics.

**Results:** At hospital discharge, many of the groups of complications were at least 10% lower than their non-complicated control group with exclusive breastfeeding. Specifically, 26.47% who experienced obstetric hemorrhages were exclusively breastfeeding at time of discharge in comparison to the control group who were at 42%. The adjusted models showed obstetric hemorrhage, pre-eclampsia, and infectious complications of pregnancy had an increased risk of using formula supplementation at time of discharge. Additionally, infectious complications of pregnancy had a higher likelihood of exclusive formula feeding at the time of discharge and use of supplementation at the 2-4 week well child visit.

**Conclusions:** We found that certain complications of pregnancy, namely infectious complications of pregnancy, pre-eclampsia, and acute posthemorrhagic anemia, are independent risk factors for affecting exclusive breastfeeding rates for lactating people after sociodemographic factors were considered. Healthcare providers should consider these complications of pregnancy and offer further assistance to lactating people.

# Constitutive Activation of STAT6 Regulates Graft-Versus-Host Disease and Preserves Graft-Versus-Tumor Effect after Allogeneic Bone Marrow Transplantation

**Presenter:** Tyler Atagozli[1,2]
**Mentor:** M. Nedim Ince, MD[1,2]
**Collaborators:** Hope Fury[1,2], Xiaoqun Guan, PhD[1,2], David Elliot, MD PhD[1,2], Bruce R. Blazar, MD[3]
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**Background**: Allogeneic bone marrow transplantation (BMT) is a potent anti-leukemic therapy where donor T cells contribute to elimination of residual cancer through the graft-versus-tumor (GVT) effect. However, donor T cells can also attack tissues of transplant recipients and cause graft-versus-host disease (GVHD). GVHD is a lethal and devastating complication of BMT, and the cellular elements of the adaptive immune system (T and B cells) play crucial roles in GVHD pathogenesis as well as the GVT effect. Acute GVHD is a T helper-1 (Th1)-mediated inflammatory process, which is regulated by activation of the Th2 pathway. STAT6 is a Th2-associated transcription factor.

**Purpose:** We investigated whether GVHD is regulated and GVT is preserved if donor T cells express a constitutively active STAT6 protein (STAT6VT).

**Methods**: We used a well-established GVHD (MHC I/II mismatch $H2^b \rightarrow H2^d$) and GVT model of BMT in mice. T cells from STAT6VT mice (MHC type: $H2^b$), which overexpress a constitutively active form of STAT6 were used as donor T lymphocytes. Splenic donor T cells from $STAT6VT^+$ ($H2^b$) mice and their wild-type nontransgenic counterparts ($STAT6VT^-$; MHC type: $H2^b$) were transferred into MHC class I and class II mismatched wildtype BALB/c ($H2^d$) recipients after myeloablative preparation with total body irradiation. Donor T cells were transferred along with T cell-depleted donor bone marrow cells (TCD-BM) in this model. Transfer of TCD-BM cells alone does not cause GVHD, but does neither exert a GVT effect. To eliminate a possible contribution of recipient T cells to GVHD and GVT, $RAG1^{-/-}$ ($H2^d$) – instead of wild-type BALB/c - recipients were used in parallel BMT studies ($RAG1^{-/-}$ recipient mice lack peripheral B and T cells, and B cells are absent during acute GVHD). GVT was quantified using bioluminescent light emission from luciferase-expressing A20 leukemia (A20-luc) cells (MHC type: $H2^d$) intravenously injected into syngeneic BALB/c ($H2^d$) or $RAG1^{-/-}$ ($H2^d$) mice within 24 hours after BMT.

**Results**: First, $STAT6VT^+$ transgenic donor T lymphocytes exerted GVT reactivity in wild-type BALB/c BMT recipient mice. Tumor-related mortality in BALB/c recipients ($H2^d$) injected with donor wildtype (WT) C57BL/6 T cell-depleted bone marrow (TCD-BM) ($H2^b$) cells was 100% compared to 0% tumor-related mortality of BALB/c recipients injected with donor WT C57BL/6 TCD-BM cells ($H2^b$) along with $STAT6VT^+$ splenic T cells ($H2^b$) ($p<0.05$). Second, $STAT6VT^+$ donor T cells did not cause GVHD or GVHD-related mortality (0% GVHD-related mortality), whereas administration of $STAT6VT^-$ wild-type donor T cells was associated with 100% GVHD-related mortality ($p<0.0001$). Third, recipient T cells can regulate GVHD, and when we used $RAG1^{-/-}$ BMT recipients to control for the GVHD-regulating effect thereof, co-transfer of $STAT6VT^+$ donor T lymphocytes regulated GVHD caused by the transfer of $STAT6VT^-$ donor T cells into $RAG1^{-/-}$ recipients. Last, co-transfer of $STAT6VT^+$ T cells with $STAT6VT^-$ T cells preserved the GVT effect in $RAG1^{-/-}$ recipients.

**Conclusions**: When constitutively expressed in donor T cells, STAT6 improves BMT outcome by not causing GVHD and preserving the GVT effect. Furthermore, STAT6 expressing donor T cells regulate GVHD after co-transfer with GVHD-causing wild-type and nontransgenic donor T cells. Our results implicate the therapeutic potential of engineering donor T cells to express a constitutively active form of STAT6 to treat leukemia without causing GVHD while preserving the GVT.

**Title:** Increased lung-protective ventilation guideline adherence and decreased ARDS incidence with protocolized mechanical ventilation

**Presenter Name: Alaina Berg**
**Mentor Name: Dr. Nicholas Mohr, MD, MS**
**Collaborators:** Erin Evans, Vivian Pham, Tyler Foley, Chloe Hlas, Mitchell Hooyer, Justin Kuhn, Boulos Nassar, Uche Okoro

**Introduction:**
Mechanical ventilation is a common, life-saving procedure, but can lead to serious complications including acute respiratory distress syndrome and oxygen toxicity. Research in lung-protective ventilation (LPV) strategies has identified a set of recommended ventilator settings for improved patient outcomes. Non-adherence to LPV guidelines has remained common.

**Purpose:** We aimed to increase adherence to LPV guidelines in the intensive care unit (ICU) setting. We hypothesized that a respiratory therapist-driven mechanical ventilation bundle could increase adherence to LPV and decrease the incidence of pulmonary complications.

**Methods:**
This was a retrospective before-after cohort study of adults admitted to critical care units at an 811-bed Midwestern academic tertiary care center between January 2011 and December 2019. The intervention involved a mechanical ventilator protocol targeting low tidal volume (<8 mL/kg predicted body weight) ventilation, appropriate positive end-expiratory pressure, limiting fraction of inspired oxygen, titrated respiratory rate, and head of the bed elevation. The protocol included training of healthcare personnel, electronic medical record templates, badge-sized protocol cards, and weekly audits of adherence. Bivariate analysis and multivariable logistic regression analysis were used to evaluate the effect of the protocol on ventilator and clinical outcomes.

**Results:**
We included 749 patients in this study, with 501 patients (66.9%) in the pre-intervention group and 248 (33.1%) in the post-intervention group. Overall adherence to all five components of LPV was higher in the post-intervention period (49% vs 36%, difference 13.4%, 95% CI 2.7-24.1). Adherence to four of the five components of LPV was higher in the post-intervention period: tidal volume (99% vs. 91%, difference 7.8%, 95% CI 3.5-12.1%), positive end-expiratory pressure, (81% vs. 69%, difference 12.3%, 95% CI 5.9 – 18.6%) the fraction of inspired oxygen (68% vs. 58%, difference 10.0%, 95% CI 3.0 – 17.1%), and respiratory rate (99% vs. 90%, difference 9.6%, 95% CI 6.5 – 12.7%). Fewer patients were diagnosed with ARDS in the post-intervention group (2.8% vs 7.2%, difference 4.4%, 95% CI 0.9-7.1%). There was no significant difference in ventilator-associated pneumonia or ICU mortality incidence.

**Conclusion:**
A respiratory-therapist-driven lung-protective ventilation protocol can increase adherence to safe mechanical ventilation standards in the ICU setting. Future work should identify barriers and implement strategies to improve adherence to positive end-expiratory pressure, fraction of inspired oxygen, and head of bed elevation guidelines.

**Image-based Assessment of Smoking Associated Emphysema Etiology**

Student: Eric Bracken
Faculty mentor: Dr. Eric A. Hoffman, PhD
Department of Radiology

## Background and Introduction

It is well established that smoking causes a variety of harmful effects to the lungs; however, there is a lack of information about the etiology of one of the hallmark impacts of smoking, COPD-associated emphysema. Tobacco smoke is the most likely cause, but not all smokers develop COPD or emphysema (30-40%), and it is found in some non-smokers. This indicates that there are genetic factors as well as environmental factors that determine an individual's chance of acquiring emphysema. Even after a smoker stops smoking, the harmful effects of previous smoking can recruit inflammatory cells to the affected areas and lead to lung injury. In the case of this regional injury, the lung will normally respond by constricting the local vasculature to provide more blood flow to better ventilated areas. This perfused blood volume (PBV) heterogeneity is counterproductive to injury repair. We hypothesize that the use of sildenafil combined with smoking cessation will decrease inflammation in the lung through restoration of perfusion by inhibiting hypoxic pulmonary vasoconstriction (HPV) in areas of smoking associated infiltrates. Previous studies have demonstrated, by use of dual energy computed tomography (DECT), that heterogeneity of pulmonary PBV (surrogate for perfusion) is significantly increased in emphysema susceptible smokers, and this heterogeneity is reduced with sildenafil. If the development of emphysema is due to failure of inherent mechanisms to block this HPV in regions of the lung injured by smoking, blocking the vasoconstriction with sildenafil may be a viable treatment option in patients that are identified early. We hypothesize that sildenafil coupled with smoking cessation will facilitate loss of inflammation characterized by a loss of CT density with scans acquired at a well-controlled lung volume (total lung capacity) and will reduce associated air trapping CT assessed air trapping.

## Methods

Smokers and non-smokers between the ages of 21 and 65 were recruited to participate in the study. The smokers were randomized to 3x/day sildenafil or placebo. The non-smokers were randomized to sildenafil 3x/day or no medication. All subjects were to have four visits (baseline, 30-day, 60-day, and 90-day) to collect vitals, blood tests, questionnaire answers, pulmonary function tests (PFT), contrast (DECT) assessment of regional pulmonary perfused blood volume and non-contrast (inspiration/expiration) CT. CT metrics include quantitative characterization of lung parenchyma including emphysema, air trapping (small airways disease), changes in lung density (index of resolution of inflammation), along with airway and vascular geometry. PFTs include spirometry and lung diffusing capacity. Blood tests provide inflammatory markers and a DNA methylation characterization of smoking and cessation.

## Results

Subject enrollment and quantitative image assessments are ongoing. Much of the summer was spent separating the arterial from venous side of the automatically extracted pulmonary vascular tree for use in the establishment of a deep learning algorithm to automate the artery/vein separation procedure. This separation is required for the evaluation of central arterial enlargement as a marker of down-stream constriction (increased resistance). Vascular and parenchymal phenotypes are being assessed in combination with the non-imaging metrics to assess the effect of sildenafil as an adjuvant to smoking cessation's reduction of lung inflammation. Smokers have been visually assessed for emphysema susceptibility with 25% susceptibility observed to date. Comparisons will be made between smokers on sildenafil, smokers on placebo, and non-smokers including diffusing capacity for carbon monoxide (DLCO), $FEV_1/FVC$, cotinine levels, DECT-derived V/Q distribution, regional perfusion heterogeneity, air trapping, change in tissue volume, and many more. We hypothesize that smokers with emphysema susceptibility will have an increased number of detectible pulmonary arterial segments due associated with arterial enlargement in response to peripheral hypoxic vasoconstriction and sildenafil will facilitate a reversal of this finding.

## Discussion

If any of the hypotheses of this study are correct, it will have offered novel insights into the disease etiology, providing new targets for disease intervention and potentially a valuable new treatment option to reduce HPV and prevent further lung injury leading to emphysema.

**Characterizing Relative Three-Dimensional Alignment of the Hip, Knee, Ankle and Foot under Physiological Upright Load. A Weight-Bearing Computed Tomography Study in Arthritic Joints and Healthy Controls**

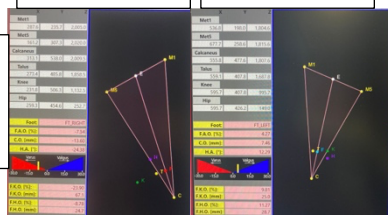
Samuel Braza, BS; Cesar de Cesar Netto, MD, PhD; Jacob Elkins, MD, PhD.

**Background:** Lower limb malignment is associated with several orthopedic disorders as either an etiological factor or as its consequence, and inability to reestablish physiological alignment when treating patients with lower limb pathologies represents a risk for residual symptoms and compensatory deformities. Lower limb alignment assessment is commonly performed using two-dimensional (2D) conventional radiographs of the entire lower extremity. Patient positioning, structures overlapping, and lack of rotational appraisal are some of the problems when utilizing these methods. Robust data was recently generated with the use of standing three-dimensional (3D) Weight Bearing Computed Tomography (WBCT) imaging in the assessment of foot and ankle orthopedic deformities. With the recent advent of WBCT imaging that allows concomitant 3D imaging of the hip, knee, ankle and foot, a more complete and multidimensional assessment of the entire overall lower limb alignment is now possible.

**Aims/Hypothesis**: The aims of this prospective study were twofold. First, to characterize the normal relative 3D alignment of the center of the Hip, Knee, and Ankle joints in relation to the weight bearing Foot Tripod in a cohort of healthy control volunteers with no lower extremity pathologies, using Weightbearing Computed Tomography (WBCT) imaging. Second, to perform the same 3D WBCT assessment in a cohort of patients with either hip osteoarthritis (HOA), knee osteoarthritis (KOA) or ankle osteoarthritis (AOA), and to compare the results between arthritic cases and controls. We hypothesized that a significant 3D malalignment with respect to the alignment of the hip-knee-ankle-foot alignment would be observed in KOA and AOA patients when compared to controls.

**Methods**: This IRB-approved, prospective comparative and controlled cohort study contained 7 HOA limbs (4 patients), 17 KOA limbs (10 patients), 7 AOA limbs (4 patients) and 10 control limbs (5 patients) that received WBCT imaging of the full lower extremity. Using multiplanar reconstruction WBCT images, 3D landmark coordinates (on X, Y, and Z planes) were manually measured by two observers. The utilized software (CubeVue; CurveBeam®) generated an automatic calculation of the Foot-Hip Offset (FHO), Foot-Knee Offset (FKO) and Foot and Ankle Offset (FAO). The center of the hip was measured at the 3D center of the femoral head and the center of the knee was measured as the center of an oval-shaped structure positioned in the most proximal full axial cut of the proximal tibia. The center of the ankle joint was defined as the most proximal and centered voxel of the talar body, and the center of the foot was defined as the bisecting line of the foot tripod point. The relationship between the center of the hip, knee and ankle joints and the bisecting line of the foot tripod was assessed and compared between HOA, KOA, AOA patients and controls. Examples of measurements for arthritic patients and controls is presented in Figure 1.

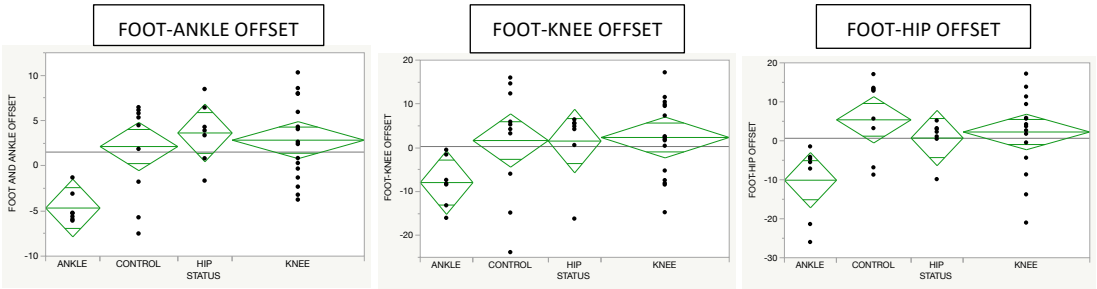
FIGURE 1




Continuous data was assessed for normality with the Shapiro-Wilk test, and variables were compared using ANOVA or Kruskal-Wallis Rank Sum. P-Values of less than 0.05 were considered significant.

**Results**: The average FAO and 95% Confidence intervals (CI) for respectively HOA, KOA, AOA and controls were respectively: 3.62% (0.4 to 6.8) (neutral), 2.8% (0.78 to 4.9) (neutral), -4.68% (-7.8 to -1.4) (varus), and 2.12% (-0.5 to 4.8) (neutral). The FAO differences were found to be significant between the groups (p=0.0077), with AOA patients being significantly different than all the other groups (Figure 2).

FIGURE 2




Similarly, the HFO was found to be significantly different between the groups (p=.002), with the following average values and 95%CI for respectively HOA, KOA, AOA and controls: 0.7% (-6.4 to 7.8), 2.3% (-2.3 to 6.8), -10.1% (-17.2 to -3.0), and 5.3% (-0.6 to 11.3). Again, the AOA patients were found to be significantly different than the other groups.

No significant differences were found between the groups when assessing the KFO (p=0.37).

**Conclusions**: In this prospective comparative cohort study, the baseline 3D lower limb alignment and relative position of the hip, knee, ankle and foot was assessed and established for the first time in the literature. When comparing 3D alignment in arthritic patients with hip, knee or ankle OA and controls, we observed that AOA was found to be the one affecting more the overall 3D alignment of the lower extremity, with no complete compensation of the deformity through the other joints, resulting in significantly different values of HFO, KFO and FAO in patients with ankle OA. Additional prospective studies with longer cohorts of patients as well as evaluation of outcomes related to the 3D measurements of HFO, KFO, and FAO are needed.

# Robust Outcomes for Hispanic Lung Transplant Recipients in the United States

**Authors:** Michelle Bremer, BS,[1,2] Omkar Rao, BS,[1] Garrick Gama, BS,[2] Eugene Golts, MD,[3] Deepa Kurup, RN,[2] Aarya Kafi, MD,[3] Christine Lin, MD,[3] Gordon Yung, MD,[3] Kamyar Afshar, DO[3]

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**Background:** Race, while a social construct, has a strong effect on a person's health. There is limited data on racial disparities within lung transplantation (LTx), especially for Hispanic recipients. Therefore, the aim of this study was to identify inequalities that may involve this population.

**Methods:** We analyzed historical data from the Organ Procurement and Transplantation Network (OPTN) and performed a retrospective review of Hispanic and Caucasian patients who underwent lung transplantation in the United States between January 1, 1990 and April 30, 2021. We compared pre-transplant health status utilizing metrics such as calculated lung allocation score (LAS) and pre-LTx diagnoses. Endpoints included length of hospital admission from date of transplant and Kaplan-Meier post-transplant survival outcomes at 30 days, one year, and three years post-LTx between groups separated by gender and ethnicity.

**Results:** During this timeframe, 2,811 Hispanics and 36,900 Caucasians underwent lung transplantation. A statistically significant difference was seen between the two groups regarding age, body mass index (BMI), type of lung transplant (bilateral versus single), and pre-transplant diagnosis. In nearly all measures, Hispanics had a significantly worse pre-transplant health status, however there were no significant differences found in any of the analyzed post-transplant outcome measures.

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**Conclusion:** Hispanics remain underrepresented among lung transplant recipients. In addition, they are transplanted at later stages in disease than Caucasians. Despite this, however, no significant difference was noted in post-transplant outcomes. Further studies should be performed to determine the underlying etiologies of these findings.

***Lrrc2, a novel target for mitochondrial function and muscle growth in Type 1 Diabetes***

*Student: Chandler Brown, M2*
*Mentor: Brian O'Neill, Internal Medicine*

Among the many metabolic changes associated with diabetes is the decline in muscle strength and mitochondrial function which can lead to further disability and ultimately mortality [**1-4**]. Interestingly, newly diagnosed insulin deficient type 1 diabetes is associated with a decrease in muscle mass and poor physical fitness [**5,6**]. In mouse models, insulin-deficiency causes decreased muscle strength and mitochondrial dysfunction via the FoxOs, which are insulin targets [**7,8**], but FoxO inhibition in other tissues can cause cancer **[9].**

We recently discovered that Lrrc2 is a downstream target of FoxOs that is exclusively expressed in striated muscle tissue, where it may localize to the mitochondria but very little is known beyond this **[10]**. When Lrrc2 is knockout out of skeletal muscle (Lrrc2 KO), oxidative soleus muscle shows hypertrophy, but mitochondrial ATP production is impaired, and ROS is increased. To determine the effect of Lrrc2 on autophagy, protein synthesis and myosin fiber content, we measured markers of these processes in gastrocnemius and soleus and of streptozotocin (STZ)-treated Lrrc2 KO mice. Although soleus was larger in Lrrc2KO mice, we saw no differences in markers of proteins synthesis (p-4EBP, p-S6), or markers of autophagy (LC3-II, K-48 Ubiquitin). In the gastrocnemius, fiber type content of type 1, 2A, and 2B/X counts were unchanged, but the cross-sectional area of the type 2a fibers in the LKO group were significantly larger than the STZ controls in the lateral gastrocnemius. We have also accessed body composition data from the DCCT to try to correlate lean mass with glycemic control, but these analyses are ongoing. After the completion of the preliminary data, we find significant contributions of LRRC2 to muscle mitochondrial function, but the effects on muscle growth and atrophy remain to be fully investigated.

**Title: Antiphospholipid antibodies – should we screen all women with recurrent pregnancy loss?**

Student: Renee Cafun
Mentor: Brad Van Voorhis MD
Collaborators: Karen Summers MPH, Brittany Bettendorf MD, Anna Merrill PhD, Sharathkumar Bhagavathi MD

Introduction: Studies show that 2-5% of couples attempting to start a family will suffer from recurrent pregnancy loss (RPL), which is defined by the American Society of Reproductive Medicine (ASRM) as two or more failed clinical pregnancies documented by ultrasonography or histopathological examination. To find the etiology of an individual's RPL, ASRM recommends an evaluation be done, including testing for antiphospholipid antibodies (APLAs). If an individual with RPL tests positive for APLAs on two separate occasions at least 12 weeks apart, a diagnosis of antiphospholipid syndrome (APS) can be made. The reported prevalence of APS in RPL patients ranges from 8-42%. However, it is suspected that this condition is often over diagnosed in practice and overestimated in studies due to lack of adherence to the revised Sapporo criteria in both labs and clinics.

Purpose: The objective of our study was to evaluate the positivity rate of confirmed APLAs in females with RPL according to the revised Sapporo criteria. To demonstrate that the APLA testing performed at our center is reliable, the positivity rate of confirmed APLAs in females seen through our Rheumatology clinic was also assessed. We also aimed to identify common features among those with confirmed APLAs that could indicate which patients should have APLA testing done rather than testing all patients being evaluated for RPL. In addition, we planned to determine the lab charges accrued in each population to assess the cost effectiveness of APLA testing in the RPL population. We hypothesized that the confirmed APLA positivity rate among those with RPL would be significantly lower that the rates reported in the literature. We also hypothesized that the RPL confirmed positivity rate would be lower than of those whose APLA testing was ordered through our center's Rheumatology clinic.

Methods: A chart review was performed on the cases in the RPL study population. All females in the RPL study population were seen through the Maternal Fetal Medicine, Reproductive Endocrinology and Infertility, and general Ob-Gyn divisions at our center and were tested for APLAs as part of their evaluation for recurrent pregnancy loss. To serve as positive controls, the results of females with APLA testing ordered through our center's Rheumatology division were reviewed and recorded. Two different subsets were identified in the group of patients who were evaluated by the Rheumatology division. Those with a chart diagnosis of systemic lupus erythematosus (SLE) or an SLE-related condition were included in the SLE control population and those without were included in the non-SLE control population.

Results: The confirmed APLA positivity rate of 1.78% among 506 RPL patients was less than the rate of 9.55% among the 199 patients with SLE and the rate of 4.06% among the 1,255 patients with non-SLE rheumatologic disease. Among those with RPL that tested positive, two had both morbid obesity and a history of thrombosis. The average titers of both isotypes (IgG and IgM) of aCL and aβ2GPI in females with SLE (73.56 GPL aCL IgG, 69.41MPL aCL IgM, 78.90 GPL aβ2GPI IgG, 72.79 MPL aβ2GPI IgM) and with non-SLE rheumatologic disease (75.14 GPL aCL IgG, 47.57 MPL aCL IgM, 79.68 GPL aβ2GPI IgG, 51.86 MPL aβ2GPI IgM) were greater that those with RPL (48.80 GPL aCL IgG, 43.18 MPL aCL IgM, 46.19 GPL aβ2GPI IgG, 38.60 MPL aβ2GPI IgM). The titers of aCL IgM and aβ2GPI IgM in those with SLE were found to be significantly greater than in those with RPL (p-values both $<0.001$). Those with non-SLE rheumatologic disease had significantly greater titers of aβ2GPI IgG (p-value of 0.008). The lab charges per confirmed positive in females with RPL was $105,278.56 while the charges per confirmed positive in females with SLE was $18,553.63.

Conclusion: The results of our study lead us to conclude that APLA testing in patients with RPL is no longer indicated. Our RPL population's APLA positivity rate (1.78%) is comparable to that of a study which evaluated APLA positivity in a population of healthy blood donors (2.72%). These low positivity rates are expected based on chance alone, calling into question the association between APLAs and RPL. Even if an RPL patient is found to have confirmed APLA positivity, there is a lack of strong evidence to demonstrate the effect of anticoagulation therapy on live birth rates. Given this and the unclear association between APLAs and recurrent miscarriages, we do not recommend the continued use of APLA testing in evaluation of RPL.

**Respiratory variability predicts severity of hypoxemia after generalized convulsive seizures**

Jack Caplan, Paula Lee, Deidre N. Dragon, Brian K. Gehlbach, George B. Richerson, Rup K. Sainju

**Background/Introduction**

Sudden Unexpected Death in Epilepsy (SUDEP) is common cause of premature death in patients with epilepsy. Although exact pathophysiological mechanism remains unclear, severe respiratory dysfunction due to generalized convulsive seizure (GCS) is likely an important mechanism. Epidemiological studies have also established occurrence and frequency of GCS as a very strong clinical risk factor for SUDEP. Peri-ictal hypoxemia is common after GCS although severe hypoxemia is less common. This has led to suggestions that peri-ictal severe hypoxemia could be a potential biomarker for SUDEP. Determinants of severe periictal hypoxemia is poorly understood. Preclinical data in mouse models of SUDEP suggest there is baseline increased respiratory rate variability, likely reflective of respiratory dysregulation, potentially predisposing them to SUDEP. A recent study in epilepsy patients has also found evidence that patients with increased baseline breathing variability tended to have severe peri-ictal hypoxemia after a GCS.

**Purpose**

This study aims to expand understanding of relationship between inter breath variability and peri-ictal hypoxemia after GCS.

**Methods**

We retrospectively reviewed multimodal physiological (EEG, EKG, respiratory) and demographic data stored at the central repository of Center for SUDEP Research (CSR). Data were collected from patients with epilepsy 18 years or older who were admitted to EMUs for video EEG study at multiple clinical hospitals around the country including the University of Iowa Hospitals and Clinics. Patients were continuously monitored on a time-synchronized video and EEG recording using a standard 10-20 system of EEG electrode placement. Respiratory monitoring consisted of chest and abdominal belts to measure effort, via respiratory inductance plethysmography. Airflow was measured by a nasal pressure transducer and an oronasal thermistor Capillary oxygen saturation ($SpO_2$) was measured on the forehead or on a fingertip.

An artifact free, interictal, 5 minutes awake recording was chosen for each subject to assess awake baseline respiratory function. Similarly, 5 minutes of interictal data was extracted during NREM sleep that established baseline respiratory function during sleep. Likewise, first 3 minutes of postictal period for all GCS will extracted to assess respiratory variability. Respiratory variability will be assessed via time series analysis of breathing frequency obtained from nasal airflow channel and expressed as variability of interval between successive inspiration a.k.a. inter-breath interval (IBI).

Mean, standard deviation and co-efficient of variation (CV) of IBI were calculated on 5 minutes recording of restful awake, NREM and REM sleep stages and immediately post GCS every minute for the first three minutes. Primary outcome was severity of peri-ictal oxygen desaturation expressed as: a) nadir peri-ictal $SpO_2$. Spearman's correlation co-efficient was calculated to determine relationship between outcome variables and independent continuous clinical variables, while student's t-test was used for categorical variables in univariate analysis.

**Results**

Total of 264 GCSs were recorded in 223 patients. Of the 264 GCSs, we analyzed 140 so far, but only 61 GCSs had adequate respiratory data to be included in preliminary analysis. Bivariate analysis showed there was a significant negative correlation between the inter-breath variability in the second minute postictal period, and the $SpO_2$ nadir post seizure (Spearman's coefficient of -0.253, $p= 0.045$). However, the $SPO_2$ nadir correlated with inter-breath variability during wakefulness (Spearman's coefficient of 0.26, $p= 0.048$).

**Conclusion**

The negative relationship between the 2$^{nd}$ minute post-ictal IBI and $SpO_2$ nadir suggests an increased respiratory dysregulation immediately after GCS likely leading to severe hypoxemia. However, the data in the first couple minutes tends to be noisy, and this could be introducing noise into the data. More work needs to be done to extend the project to all the GCSs with adequate respiratory data, and to correlate the hypoxemia with other demographic and clinical variables.

# Utilization of Ketogenic Diet Worsens Visual and Motor-Sensory Deficits in An Animal Model of Multiple Sclerosis

Erin N. Capper, Jeffrey J. Anders, Benjamin W. Elwood, Randy H. Kardon, Oliver W. Gramlich

Introduction: Multiple sclerosis (MS) is a chronic neurodegenerative condition characterized by demyelination of axons in the central nervous system (CNS) resulting in sensory-motor deficits and vision loss. Damage to the CNS causes most patients with MS to suffer retinal nerve fiber layer (RNFL) loss and impaired electrical function with approximately 20% of people displaying optic neuritis as the initial presenting symptom. Because conflicting results on the benefits of a ketogenic diet in neurodegenerative diseases are published, the purpose of this study was to determine the effects of the ketogenic diet on visual function and structure in relation to timing of its implementation in an experimental autoimmune encephalomyelitis (EAE) mouse model of MS.

Methods: EAE was induced in the 80 female C57BL/6J by immunization with $MOG_{33-55}$, complete Freund's Adjuvant, and pertussis toxin. Cohorts of EAE induced mice (n=20/group) were assigned to stay on the standard rodent chow (EAE) or to start the ketogenic diet (KD) either 2 weeks before EAE induction (preconditioning (pre)), at EAE induction (prophylactic (pro)), or at the onset of symptoms (late intervention (late)). Another 16 mice served as a naïve control group. Mice were scored every day for motor-sensory impairments using a mobility scale (0=normal to 5=death). Visual acuity was tested weekly throughout the 42 days using optokinetic responses (OKR), and RNFL thickness was measured at baseline, day 21, and day 42. Pattern electroretinography (pERG) and visual evoked potentials (VEP) were recorded at the end of the experiment before the retinas, optic nerves, brain, and spinal cord of each mouse were harvested for subsequent analysis. All data were analyzed using one- and two- way ANOVA followed by post hoc tests.

Results: EAE animals from the preconditioned ketogenic diet groups showed significantly worse motor-sensory impairment relative to EAE controls (Area under curve EAE score: EAE: 58±2, EAE + pre KD: 68±3, $p<0.001$; EAE + pro KD: 60±3, $p=0.09$; EAE + late KD: 58±3). Similarly, visual acuity data showed worse OKR tracking in the preconditioned ketogenic diet group (0.23±0.05 cycles/degree;) compared to naïve (0.38±0.03 cycles/degree, $p<0.0001$) and EAE controls (0.26±0.05 cycles/degree; $p=0.024$). There was no significant difference between the standard diet EAE controls compared to the prophylactic (0.24±0.06 cycles/degree) and late intervention group (0.25±0.05 cycles/degree), but all three EAE groups had significantly lower visual acuity and EAE scores than the naïve group ($p<0.0001$). In comparison to naïve mice, average RNFL thickness decreased significantly after 42 days in all EAE induced mice (naïve: 69±2µm vs. EAE: 66±4µm; $p=0.001$, EAE + pre KD: 66±4µm; $p=0.002$, EAE + pro KD: 67±4µm; $p=0.02$, EAE + late KD: 66±3µm; $p=0.001$) whereas differences between these four EAE induced groups were not significant. Furthermore, 42 days after EAE induction, all EAE mice showed changes in pERG amplitudes and alterations in optic nerve conduction speed when compared to naïve animals.

Conclusion: This study identified that implementing a ketogenic diet negatively influenced motor-sensory and visual function, and that preconditioning the mice with the diet before EAE induction resulted in the worst structural and functional outcome. These data suggest that a ketogenic diet should not be recommended for patients with MS. There is evidence that a ketogenic diet fosters low-grade systemic inflammation, thus cytokine levels and grade of cell infiltration in the anterior visual pathway will be analyzed in remaining EAE samples in a subsequent study.

**Characteristics of patients who develop cell checkpoint inhibitor BP compared to classic onset BP.**

**Authors:** Sahil Chawla, Maryam Fakhimi, Anthony M. Fleck, Janet A. Fairley, and Kelly N. Messingham

**Background:** Bullous pemphigoid (BP) is an antibody-mediated blistering disease targeting BP180, a hemidesmosomal protein required for epidermal adhesion. Patients present with a pruritic rash followed by fluid-filled blisters that can be localized or distributed widely on the body. Broad-based immunosuppression is the standard therapy for BP, since the basic mechanisms of autoantibody development are not understood. While the vast majority of BP cases are of unknown etiology, the incidence is highly enriched in patients treated with immune checkpoint inhibitors, which are used to promote anti-tumor activity by downregulating immunotolerance mechanisms. It is not understood if the same mechanisms are responsible for the development of classic BP and drug-induced BP.

**Purpose:** To compare the clinical and immunologic characteristics of patients with classic BP and those who developed BP while undergoing treatment with checkpoint inhibitors.

**Methods:** This project was divided into two parts. In the first, a systemic literature review identified case reports and case series describing patient who developed BP while taking nivolumab, pembrolizumab, cemiplimab, ipilimumab, atezolizumab, avelumab, or durvalumab. 51 articles from 2017 – 2022 were included with a total of 121 patients studied. In the second part (IRB#202109472), we evaluated antibody profiles by ELISA in 4 groups of patients: checkpoint-inhibitor BP (n=11), classic BP (n=24), cell checkpoint inhibitors but no BP (n=11), healthy controls (n=15).

**Results:** Of the 121 cases of cell checkpoint inhibitor BP, 89 (74%) were male and 32 (26%) were female, with an average age of onset of 74 years old. Most checkpoint inhibitor BP cases occurred in patients taking anti-PD1 inhibitors, nivolumab and pembrolizumab, and to a lesser extent, anti-PD-L1 drugs, atezolizumab and durvalumab. The median onset time for BP was shortest (6 wks) in patients treated with ipilimumab and longest (72 wks) for those treated with atezolizumab. Similar to classic BP, immunofluorescence was the most common diagnostic technique, with most patients positive for linear Ig (G or A) and C3 along the dermoepidermal junction and histologic staining showed dermal eosinophilia. In most cases, IgG specific for BP autoantigens, BP180 and BP230, or total IgE levels, were also reported. In ongoing work, these characteristics will be compared to a large cohort of patients with classic BP.

When autoantibody profiles were compared in our 4 groups of patients, there was no difference in the level of BP180 or BP230-specific IgG or BP180-specific IgE. However, total circulating IgE was higher in patients with classic BP, compared to those with cell-checkpoint (PD-1) inhibitor BP (Kruskal-Wallis test followed by Dunn's multiple comparisons test, adjusted p-value = 0.0220).

**Conclusion:** This study indicates that most characteristics of patients who develop BP while being treated with cell checkpoint inhibitors are like those with classic BP. Differences were observed in disease prevalence in males vs. females and serum levels of total IgE. Further study is needed to understand the significance of these findings.

**The Role of Social Touch Neurons in Stress Resilience**

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[1]Carver College of Medicine, The University of Iowa, [2]Department of Molecular Physiology and Biophysics, The University of Iowa, [3]Iowa Neuroscience Institute, Carver College of Medicine, The University of Iowa, [4]Neuroscience Graduate Program, The University of Iowa, [5]Department of Statistics and Actuarial Science, The University of Iowa, [6]Institute for Neurological Science, University of Pennsylvania, [7]Zuckerman Mind Brain Behavior Institute, Columbia University

Stress can have psychological, physical, and emotional effects on the body and behavior. While stress is a major risk factor for disease onset for various psychiatric disorders, the impacts of stress can be buffered by social touch. However, the skin-brain pathways underlying this stress resilience are not known. To study these pathways, we used a mouse model with early life genetic ablation of Mrgprb4-lineage touch neurons (B4 KO). In mice, these neurons project exclusively to the hairy skin and are known to respond to social touch stimuli, such as during social-grooming or huddling. B4 KO mice showed normal baseline behaviors, but under sub-chronic stress conditions displayed an anxiety and depressive-like phenotype compared to control mice. To investigate potential mechanisms underlying this stress-vulnerable response, we performed multi-circuit neurophysiological recordings across brain regions involved in affect and stress vulnerability, during which we simultaneously collected local field potential (LFP) and single unit firing data. Under baseline conditions, we observed altered LFP signal directionality in B4 KO mice, particularly between the ventral tegmentum area (VTA) and the nucleus accumbens (NAc) brain regions. Under sub-chronic stress conditions, we observed altered LFP power in the NAc at the 1-8 Hz frequency range in the B4 KO mice. We then analyzed the single unit firing data by sorting cells within the VTA and NAc to study the firing behavior of individual neurons, and with these individual cell data can now perform more complex analyses to gain further mechanistic insight. Our studies altogether suggest that sensory neurons in the skin are involved in networks with the brain, particularly in the VTA-NAc pathway, to promote stress resilience.

**Three-Dimensional Weight Bearing CT Assessment of Lesser Toe Deformities. A Case-Control Study.**

Student: Nathan Chen, M1
Mentor: Dr. Cesar de Cesar Netto, MD, PhD – Department of Orthopedics and Rehabilitation

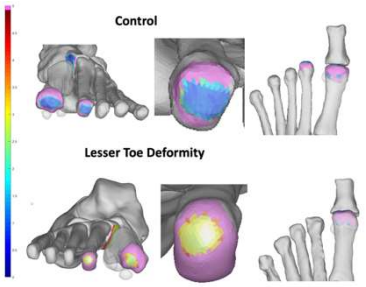
## Introduction

Lesser toe deformities (LTD) have been challenging clinical scenarios ever since the basic understanding of the disease's true physiopathology, its proper early diagnosis, and the appropriate treatment. Anatomical variations of the lesser metatarsals, particularly increased length and malrotation, have been demonstrated to potentially predispose patients to overload, plantar plate degeneration, and progression of a LTD. Assessment of lesser MTPJ characteristics is usually performed using clinical assessment and conventional 2D radiographs. Three-dimensional anatomical assessment using weight-bearing computed tomography (WBCT) measurements might depict particular imaging patterns. It can also demonstrate joint interactions by applying bone segmentation, coverage, and distance mapping. This technology, already established for several other foot and ankle conditions, might help the understanding and better management of patients with LTD.

## Aim/Hypothesis

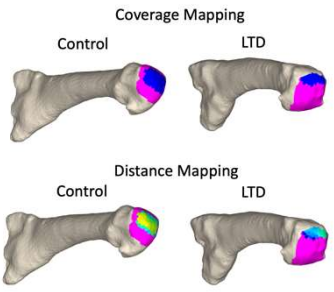
The objective of this study is to evaluate lesser metatarsophalangeal joint's (MTPJ) anatomy as well as the pattern of articular interface and severity of subluxation of the MTPJ in patients with LTD and in a cohort of healthy volunteers, using WBCT images and distance mapping assessment. Our hypothesis is that pronounced lesser metatarsal malrotation, plantar inclination, dorsal subluxation, and elongation will be present in LTD when compared to controls.

## Methods




In this retrospective IRB-approved case-control study set at the University of Iowa Department of Orthopedics and Rehabilitation, ten patients (ages 18 to 75) diagnosed with a second and/or third LTD and ten healthy control volunteers with no foot and ankle disorders that underwent a WBCT as standard of care were included (PedCat®, LLC, Warrington, PA, USA). Overall foot alignment and lesser metatarsal anatomical characteristics were evaluated using 3D measurements, such as the Foot and Ankle Offset (FAO), intermetatarsal angles, head protrusion (Coughlin), and osteoarthritis grade (Menz) that considered midfoot and forefoot joints. The 3D positioning of the lesser metatarsal heads was also assessed by harvesting the 3D coordinates (planes X, Y and Z) of the weightbearing and most distal points of the lesser metatarsal heads as well as the center of the tarsometatarsal joints, allowing assessment of the length and relative positioning of the lesser metatarsals. Bone segmentation was performed using a dedicated software and distance and coverage maps were created for the second, third, and fourth MTPJ. For a more accurate assessment of distance and coverage maps, joint surfaces were divided in four quadrants. Distance measurements were defined as the distance along the normal direction of vectors projected from one surface to the opposing surface in each joint. Maps were colored-coded to highlight regions of interest. Coverage maps were created using measured distances to highlight areas of proper joint interaction and joint subluxation (Figure). Measured variables were compared among LTD and control groups. Normality was determined using the Shapiro-Wilk Test. Values for data that were normally distributed were calculated using a two-tailed Student's T-test. For non-normal data, the Mann-Whitney-Wilcoxon U test was used. Statistical significance was established for p-values under 0.05 with a 95% confidence interval.

## Results




Mean age (53.79; SD: 8.09 in LTD and 29.60; SD 16.37 in controls) and BMI (29.60; SD 5.50 in LTD and 30.98; SD 8.29 in controls) were similar between the two groups (ps>0.15). The similarity was maintained for the FAO, axial angles, and osteoarthritis grade (ps>0.35). Considering WBCT anatomical measurements, the LTD group demonstrated higher first metatarsal head pronation (-16.93 vs -9.27, p=0.027). Although LTD patients demonstrated a lower rotation at the base and at the head, as well as a higher length in the axial and sagittal planes, these differences did not reach statistical significancy (ps>0.07). When comparing MTPJ coverage mapping, the dorsolateral aspect of the LTD 4$^{th}$ heads (-0.558%; p=0.042) and the plantarlateral portion of the 4$^{th}$ bases (-0.163%; p=0.032) presented more uncoverage than controls. Overall coverages of all LTD heads were lower than controls, while not significant (ps>0.24). Mean distances across the dorsomedial and platarmedial aspects of the 3$^{rd}$ and 4$^{th}$ metatarsal heads increased in the diseased population (0.273%; p=0.046 and 0.405%; p=0.007). In the LTD population, distances from head to phalanx were higher and lower from base to cuneiforms. However, these were still not statically different (ps>0.061).

## Conclusion

Anatomical forefoot characteristics, such as metatarsal inclination, length and rotation were not different in patients sustaining LTD. Patients having lesser toe deformities demonstrate distinctive metatarsal dispositions when compared to controls. Distance and coverage mapping were able to differentiate patients from controls in some regions, a property that can be used as an earlier disease marker and a likely reference for treatment strategies evaluations. Our hope is that this technology can optimize the diagnosis, staging, and assessment of both treatment and outcomes in lesser toe deformities. Additional appropriately sized prospective studies are needed to further depict smaller, but potentially clinically important, differences.

**Phenotypic and Transcriptional Characterization of T cell subsets in Bullous Pemphigoid Patients**

**Authors:** Tian Y. (Tracy) Chen, Maryam Fakhimi, Tyler P. Crowe, Janet A. Fairley, Kelly N. Messingham

**Background:** Bullous pemphigoid (BP) is a blistering disease of the elderly that is mediated by autoantibodies targeting Collagen XVII/BP180. Since the basic mechanisms of disease are not understood, standard treatment is broad-based immunosuppression with steroids, which is associated with significant morbidity and mortality.

Autoimmunity originates when central and peripheral tolerance mechanisms fail. In peripheral tolerance, autoreactive T cells are suppressed or deleted through interaction with inhibitory cell surface markers expressed on dendritic cells and/or regulatory T cells (Tregs). In BP, the immunologic alterations leading to autoantibody development remain undefined.

**Purpose:** We hypothesize that the development of BP lesions is dependent on phenotypic and functional alterations in T cell populations, such as Tregs.

**Methods:** Peripheral blood mononuclear cells (PBMCs) were collected from 20 BP patients (45% female, mean age 76.1±10.7, range 45.5-93.4) and 24 control patients (29% female, mean age 77.0±8.3, range 57-90.3). CD4+ T cells were purified, and RNA was extracted and reverse transcribed into cDNA. RT-qPCR was performed with PCR primers directed against a panel of human T-cell anergy and immune tolerance genes. T cell subsets and their expression of various activation and exhaustion markers were analyzed by multicolor flow cytometry. In addition, T cell receptor (TCR) Vβ repertoire was evaluated due to the high rate (~90%) of *Staphylococcus aureus* colonization in BP and the ability of staphylococcal toxins to trigger TCR Vβ-mediated activation and expansion.

**Results:** Gene expression of immunotolerance markers, IL2RA, CTLA4, and CD40L, was downregulated in BP samples ($p<0.05$). On the other hand, the frequencies of T cell subsets, CD4+ T cells and FOXP3+ Helios+ Treg cells, were similar in BP and controls. Immunotolerance markers like CTLA-4 and Ki-67 were also similar in BP and controls. Interestingly, while TCR Vβ repertoire utilization by CD4+ T cells or FOXP3+ Helios+ Treg cells were similar in BP patients and controls, the TCR Vβ repertoire utilization differed between T cell subsets (CD4+ T cells vs. FOXP3+ Helios+ Tregs).

**Conclusion:** This study identified decreased expression of immunotolerance genes, but no change in the frequency of CD4+ T cells or Tregs. This suggests that the loss of tolerance in BP may be associated with qualitative difference in T cell subsets. Further study is needed to understand how these changes impact peripheral T cell homeostasis and their relevance to cutaneous T cell function.

# Diabetes Device Downloading during Adolescence and Glycemic Control

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**Background:** Regular retrospective review of glucose patterns is an important aspect of type 1 diabetes (T1D) management. Continuous glucose monitors (CGM) facilitate retrospective review by robustly capturing glucose data and generating user-friendly reports. Despite an increase in CGM usage, mean HbA1c among adolescents has increased in the last decade and remains above treatment goal, which increases the risk of long-term diabetes complications. The aim of this study was to determine factors associated with retrospective data review among adolescents, with a secondary aim of determining characteristics associated with improved glycemic control among adolescents who perform regular retrospective review.

**Methods:** We conducted a cross-sectional survey of adolescents aged 12-18 with T1D in conjunction with review of the associated electronic medical record and CGM data. The survey collected participants' demographic information and their habits and attitudes associated with retrospective review and ensuant insulin adjustment. It also included 3 validated surveys, including the Hypoglycemia Fear Survey (HFS), Institute of Medicine's Social and Behavioral Determinants of Health survey, and Problem Areas in Diabetes questionnaire (PAID).

**Results:** The survey will close on 8/30/2022, which represents 12 weeks of data collection. The American Diabetes Association recommends that children with T1D are seen in clinic every 3 months; therefore, this data collection period ensured universal sampling of eligible individuals. 133 of 188 eligible individuals have responded thus far (70%). Responders were similar to non-responders with regards to sex and insurance status, but had lower median HbA1c (7.35 v 8.0, p=0.006). Preliminary analysis found no association between retrospective review and glycemic control as measured by HbA1c. This may be explained by another preliminary finding, namely that increased HFS scores were associated with retrospective review. Further analysis will consider demographic information (age, sex, race, insurance type, duration of diabetes, access to technology) as well as CGM metrics including time in range (TIR), time below range (TBR), glucose management indicator (GMI), and coefficient of variability (CV). It will also assess for the number of insulin adjustments made in response to retrospective review.

**Conclusions:** Retrospective review of glucose data does not appear to be associated with improved glycemic control. There is conflicting evidence regarding the impact of fear of hypoglycemia on overall glycemic control. Interestingly, retrospective reviewers scored higher on the HFS, suggesting that perhaps avoidance of hypoglycemia rather than mitigation of hyperglycemia is what prompts retrospective review in adolescents. We noted similar findings in a study of adult caregivers of children with T1D, suggesting that clinical training and patient education directed at optimization of retrospective review would be a beneficial adjunct to CGM. Automated pattern recognition software may help guide insulin adjustments in those with elevated hypoglycemia fear.

**Targeting CXCR4 and Thioredoxin Reductase in High Grade Neuroendocrine Tumors & Neuroendocrine Carcinomas**

Student: Keegan Christensen, M2
Mentor: Doug Spitz and Melissa Fath, Radiation Oncology

**Introduction/Background:** Atypical lung carcinoids and lung neuroendocrine carcinomas (NECs) are currently incurable with most patients dying of disease within five years after diagnosis, therefore there is a critical need for a new therapeutic strategy. The majority of these cancers express the G protein coupled receptor C-X-C chemokine receptor 4 (CXCR4), as demonstrated with immunohistochemistry, making CXCR4 an attractive target for cancer diagnosis and treatment. Peptide Receptor Radionuclide Therapy (PRRT) features a radioactive nuclide conjugated to a peptide ligand with high affinity for a receptor on cancer cells. CXCR4 can be targeted with pentixather radiolabaled with Pb212 for alpha emitting radionuclide therapy. Alpha particles produce dense ionization tracks and damage cytosolic structures such as mitochondria, leading to the generation of reactive oxygen species (ROS) such as superoxide ($O_2^{\bullet -}$) and hydroperoxides ($H_2O_2$ and ROOH) that induce metabolic oxidative stress in targeted cancer cells. Auranofin (Aur) inhibits thioredoxin reductase, which disrupts hydroperoxide metabolism through peroxiredoxins leading to further increases in oxidative damage in the selectively targeted cancer cells. **Hypothesis:** Inhibition of hydroperoxide metabolism using Aur can enhance therapeutic efficacy of 212Pb-pentixather in preclinical models of lung NETs and NECs. **Results:** qRT-PCR, flow cytometry and immunohistochemistry performed on different NETS and NEC lung cell lines, determined that the majority moderately or highly express CXCR4. In a dose escalation experiment, the minimal effective dose of Aur that inhibits 50-70% of thioredoxin reductase activity, without causing toxicity, in DMS273 mouse xenograft model was determined to be 4 mg/kg intraperitoneal once a day. Mice bearing DMS273 small cell lung cancer xenograft were treated with 1.5, 3 or 6 µCu/g 212Pb-pentixather with and without treatment with Aur. A trend test was performed on both increasing dose of 212Pb-Pent and the addition of Aur, and both were found to cause a significant ($p<0.01$) delay in growth. Preliminary analysis of toxicity was based on the change in body weights of mice, complete blood counts (CBC), serum alanine aminotransferase. There were no significant changes in any parameter tested. Radiation dosimetry was performed using quantitative SPECT/CT imaging with Pb203-pentixather in a separate murine cohort, with average absorbed doses of 0.133 Gy/µCi (liver), 0.098 Gy/µCi (kidneys), 0.013 Gy/µCi (H292), 0.028 Gy/µCi (DMS53), 0.057 Gy/µCi (DMS273), and 0.096 Gy/µCi (H69AR). **Conclusion**: The use of 212Pb based alpha-particle therapy to target CXCR4 on SCLC showed efficacy in a dose dependent manner. Combination therapy with Aur further delayed tumor growth without significant toxicity concerns. Preclinical studies indicate that CXCR4 could be used for targeted radionuclide theragnostics using Pb212/Pb203-pentixather.

We greatly appreciate the financial support provided from the National Cancer Institute: R01182804, P01CA217797, R50CA243693, SPORE: P50CA174521

**Evaluating Colony Formation Efficiency (CFE) of Basal Cells Along Different Levels of the Ferret Airway**

Carolina Chu, M2
Mentors: Dr. Kalpaj R. Parekh, MBBS, Dr. Thomas Lynch, PhD, Vitaly Ievlev, Dr. Kyle Freischlag, MD, Caitlyn Gries

*Background*

Chronic Lung Allograft Dysfunction (CLAD) is one of the major complications that hinder long term success of lung transplants. An interplay of multiple factors contributes to CLAD development, but of interest is the role of airway stem cells. The Parekh Lab has demonstrated that, in CLAD, there is widespread destruction of airway stem cells/basal cells (BCs) with near complete depletion of BCs in the distal airway, along with a global decline in proliferative capacity. To better understand these stem cells, optimization of lung epithelial cell culture must be achieved.

*Hypothesis*

We hypothesize that there is distinct variation in the amount of BCs in the proximal vs. distal airways and that the stem cells from different levels of the airway have varying colony forming efficiencies (CFE) that may impact their ability to repair damage.

*Methods*

Naïve ferret airways were isolated, divided into distinct levels (trachea, carina, mainstem bronchus, 1$^{st}$-3$^{rd}$ order bronchioles), and then both cultured initially into a CFE (CFE P0) and placed first in Pneumacult Ex+ media then subsequently cultured into CFE (CFE P1). Two separate plates were done for each condition with technical duplicates. One plate under each condition was then stained for immunofluorescence using BC specific markers (K5, K14, P63) with the other plate used to probe for BC markers (K5) via qPCR. Colony forming efficiency (CFE) was determined by number of total colonies/number of cells seeded.

*Results*

A successful protocol of culturing lung epithelial cells was optimized. Data showed decreasing CFE in the distal airways/tertiary branching bronchioles (n=7). qPCR data also showed decreasing expression of K5 in the BCs from distal airways (n=4). Data from cells that had been initially cultured in Pneumacult Ex+ media did not show differences in CFE along the airways (n=7). However, qPCR data continued to show decreasing expression of K5 in BCs isolated from proximal vs. distal airways (n=3).

*Discussion*

During initial seeding of cells into CFE P0, the proportion of proliferative cells along the airway most likely differed, thus leading to decreased CFE in the distal airways. However, when BCs are exposed to Pneumacult Ex+, the media may enhance the survival of existing populations of stem cells, leading to a higher/more equal proportion of proliferative cells when seeding into CFE P1 and equal CFE. There was no difference in CFE despite apparent differences between stem cell populations at different levels of the airway as indicated by varying expression levels of K5. Thus, K5 expression levels may indicate the “identity” of various BCs, suggesting that there are different populations of lung stem cells that exist in varying proportions and predominance along the airways. Therefore, CFE P1 data showing no difference in CFE but continuing to show decreased K5 expression in the distal airway may indicate that the BC populations along the airway may not be identical but have similar proliferative capacity.

**Current screening practices for perinatal mood and anxiety disorders and perinatal substance use disorders**

Kaitlyn Clevenger M2, Stephanie Radke MD, Kelli Rickman PhD, Nancy Weathers

## Background

Perinatal mood and anxiety disorders (PMAD) are one of the most common mental health conditions experienced by women of child-bearing age. It is estimated that one in seven women (14%) will experience depression during the perinatal period, but some estimates are as high as 25%. As for anxiety, it is estimated between 13-21% of women will have prenatal anxiety and 11-17% will have postpartum anxiety, with many women experiencing both. Perinatal substance use disorders are not as common, but prevalence rates are increasing. Additionally, PMAD are considered one of the most underdiagnosed obstetrical complications in the United States, partly due to inconsistent or absent screening practices among obstetrical providers. Underdiagnosis due to improper screening is concerning because untreated PMAD and perinatal SUD can have severe consequences for both mother and child.

## Purpose

The purpose of this study was to characterize the current PMAD and perinatal SUD screening practices among Iowa obstetrical providers, identify the clinical policies and procedures pertaining to PMAD and perinatal SUD screening throughout the state, and identify key barriers and facilitators to universal screening for PMAD and perinatal SUD.

## Methods

This study had two phases. The first phase included a series of interviews conducted with Iowa obstetrical providers about their current screening practices and policies implemented in their clinics. These interviews responses were analyzed and aided in the development of the second phase. The second phase of this study utilized the information learned from the provider surveys, the relevant published literature, and the community advisory board to generate a survey to be distributed to healthcare providers in Iowa that treat PMAD and perinatal SUD.

## Results

While the first phase of this study has been completed, the survey created during the second phase is still open and collecting responses from providers. It is expected that the results obtained from the survey will be utilized in the creation of an executive summary with recommendations on needs that must be implemented for universal screening of PMAD and perinatal SUD which will be presented to the Iowa Department of Public Health.

## Conclusion

Mental health disorders and substance use disorders among pregnant and postpartum women have been classified as contributing factors to pregnancy-related deaths in Iowa, thereby signifying a need to improve the identification and management of those disorders. The first step toward improvement is to identify current screening practices among providers because, as previous research has shown, they vary widely. Understanding the current screening practices along with the perceived barriers will eventually yield recommendations on how to proceed to ensure the proper screening steps are being taken to optimize future treatment of PMAD and perinatal SUD.

**ABSTRACT**

**Title:** Defining Relative Amount of Myocardium at Risk for CABG Patients
**Author:** Inna Couri, Daniel Conway, Dr. Arun Singhal

**Background/Introduction**
Coronary artery disease (CAD) affects about 20.1 million adults aged 20 and older and is the leading cause of death in the United States. While stable CAD may be treated with pharmacotherapy, select patients may require revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting surgery (CABG). The 2021 ACC/AHA/SCAI guidelines for coronary artery revascularization state that "The more myocardium is at risk, the greater is the survival advantage of revascularization over medical therapy." However, there is no definition as to what a significant amount of myocardium would constitute for this recommendation, and thus there is no clear standard for identifying which patients would be better suited for revascularization over medical management. Therefore, a system is needed in which the amount of myocardium at risk can be approximated. This will allow for an objective determination of the impact of vessel abnormalities and define significance of coronary artery disease for potential CABG patients. Though previous systems have attempted similar feats, they have focused on stent-based repair and are not applicable for surgery patients.

**Purpose of Study**
The purpose of the study is to create a system to correlate coronary artery anatomy with myocardium of the left ventricle with a numerical score using objective data from cardiac catheterization films. We aim to create such a system that can be applied to all patients and provides reproducible results that are independent of the observer.

**Methods**
We created a system to assign numerical point values to the major vessels supplying the left ventricle that approximated the amount of myocardium supplied by each. Briefly, the observer utilizes cardiac catheterization films to compare relative vessel lengths and anatomical landmarks of the left ventricle and calculates corresponding myocardial supply. The system was applied to 75 different patients and scored independently by two observers. The differences in the scores were analyzed using average difference for each of the three main vessel systems (left anterior descending, circumflex, and right coronary artery).

**Results**
The system was applied to 75 different patients, and it was found that it could be used on all films. Upon validation of the system, the inter-observer difference in scoring was found to be approximately 5%.

**Conclusion/Discussion**
A system to define myocardial supply of the left ventricle with a numerical score was developed and validated. It has been shown that it can be used on any patient and that the results of the score are independent of the user. The major limitation of the study thus far is the limited number of patients we have tested the system on, so from here we seek to continue to validate the results with additional expert observers. From there, we eventually seek to investigate the relationship between patient scores and outcomes of CABG surgery.

# Investigation of neuroinflammation in hemophilia A

Kendall Cornick, M2, Danielle York, Janice Staber, MD

*Introduction:*
Hemophilia A (HA) is a genetic bleeding disorder characterized by a lack of factor VIII (FVIII), a protein important in producing a clot. Current treatment, such as prophylactic FVIII replacement therapy, helps prevent uncontrolled bleeding and subsequent irreversible joint damage. However, individuals with HA are still at an increased risk of neuropsychiatric disorders. These observed disorders could be a result of neuroinflammation that is insufficiently prevented by the current treatment. Previous microglial studies in the Staber lab suggest that neuroinflammation is indeed present in the HA mouse model, however there is a need to better understand the mechanism driving this process.

*Purpose:* To understand the mechanism of neuroinflammation occurring in a HA mouse model, with a specific focus on how the pro-inflammatory and pro-repair pathways function in specific brain regions.

*Methods:*
Brain regions, specifically the brainstem, cerebellum, cortex, and hippocampus, were harvested from HA and wild-type mice at approx. 6 months of age. RNA was isolated from each region and converted to cDNA. Gene expression of the pro-inflammatory pathway (IL-1β, IL-6, TNFα, iNOS) and pro-repair pathway (IL-10, TGFβ, CD206, IL-4Rα) were measured by RT-qPCR assays. Statistically significant differences in gene expression between HA mice and WT mice were evaluated via two-way ANOVA in GraphPad Prism utilizing a Sidak test for multiple comparisons.

*Results:*
Among our genes of interest, IL-10, in the pro-repair pathway, was significantly upregulated in the brainstem of HA mice. Additionally, there appeared to be patterns of upregulation in various pro-inflammatory and pro-repair genes including iNOS in the brainstem, IL-10 in the cortex, IL-6 in the hippocampus, and TGF- β, IL-4Rα, and IL-6 in the cerebellum.

*Discussion:*
Microglia, the primary immune cells of the brain, can adopt pro-inflammatory or pro-repair states. Characterizing the balance between those two states is critical in understanding the neurological implications of HA and to help narrow the list of future targets for therapeutics. This pilot study revealed many trends in gene expression that we will continue to investigate as we increase the sample size and expand upon the ages of mice included.

# THE EFFECT OF PREOPERATIVE TAMSULOSIN ON INTRA-OPERATIVE OUTCOMES IN CHILDREN UNDERGOING URETEROSCOPY TO TREAT KIDNEY STONES

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**Background:**

The past two decades have seen a 4-10% annual increase of pediatric nephrolithiasis. This rise has been matched with an increased interest for advances into the surgical and medical management of pediatric stone disease. Tamsulosin is an oral alpha adrenergic receptor antagonist, which may improve ureteral relaxation. Tamsulosin can be used to help with medical expulsion therapy (MET) for ureteral stones in children and adults. It is common practice for patients who present with a ureteral stone to be placed on MET, as this can help improve the ability to pass the stone without the need for surgical intervention. If a stone is unable to be passed then operative management, usually in the form of ureteroscopy (URS), is necessary. URS is a surgical operation where a ureteroscope is passed through the urethra and the bladder and into the ureter to locate, fragment, and remove the stone. At times, the passage of the ureteroscope into the ureter is limited due to anatomic differences in the ureter's size and diameter. As tamsulosin helps relax the ureter, studies in adults have shown that preoperative use of tamsulosin increases the success of being able to safely perform ureteroscopy, and gain access to the ureter. The effect of preoperative tamsulosin has not yet been fully evaluated in children undergoing URS.

The goal of this retrospective study is to evaluate the effect of tamsulosin in children undergoing URS. We hypothesize that tamsulosin will improve the success rate of pediatric ureteroscopy.

**Materials and Methods:**

We retrospectively reviewed the charts of all pediatric patients (0 – 18 years old) who had undergone ureteroscopy from January 2013 to March 2022 at the University of Iowa. Patients were divided into two groups: (1) Those taking tamsulosin prior to URS and (2) Those not taking tamsulosin. Patient demographics and stone characteristics were evaluated. In addition, we collected data regarding our ability to gain ureteroscopic access to the ureter, the need to dilate the ureter in order to gain ureteroscopic access to the ureter, and the need to place a ureteral stent at the conclusion of the case. Statistical analyses were done using Fisher's Exact Test for categorical variables, and Wilcoxon rank sum tests for continuous variables. Categorical measures were summarized using counts and percentages, while continuous measures were summarized using medians and interquartile ranges. P-values were calculated to test whether there was a significant difference between the patients who received tamsulosin and the patients who did not. A p-value of 0.05 was considered statistically significant.

**Results:**

We identified 75 patients who underwent ureteroscopy. Ten patients were placed into the "Tamsulosin Cohort," and 65 patients were placed into the "No Tamsulosin Cohort." Patient demographic information was similar between groups. Overall, successful ureteral access occurred in 9 of 10 patients (90%) who had received preoperative tamsulosin, and 53 of 65 (82%) in those that had not ($p > 0.9$). The tamsulosin group had a lower percentage of cases that required ureteral dilation (30% vs. 55%, $p = 0.2$) during surgery, and less frequency needed a stent placed after the procedure (80% vs. 82%, $p > 0.9$).

**Conclusion:**

Despite improved trends, preoperative tamsulosin did not significantly improve successful ureteral access, reduce the need for ureteral dilation during URS, or reduce the rate of stent placement after URS. Further studies with a larger cohort of pediatric patients undergoing URS are necessary and planned to determine the true effect tamsulosin has on pediatric URS.

# Examining the Role of Cortical CGRP Neurons in Migraine

Abby Davison, Andy Russo, Ph.D., Levi Sowers, Ph.D.

## Introduction

The underlying pathophysiology of migraine is poorly understood and there remains an unmet clinical need for a greater variety and specificity of treatments. Since calcitonin gene-related peptide (CGRP) is well known to be sufficient and necessary in migraine, we aimed to increase our understanding of the circuitry of CGRP neurons in the brain. Previous studies in mice have demonstrated the importance of the posterior thalamic region (PoT) in producing a migraine-like phenotype, particularly photophobia. Additionally, retro-orbital injections in mice, coupled with tissue clearing methods and light sheet microscopy, allowed us to visualize brain-wide expression of a virus in Calca-Cre (CGRP) neurons. Considerable expression was shown in the primary visual cortex (V1).

## Hypothesis

We hypothesized that neural connections from the PoT to V1 are involved in the induction of light aversion in a mouse model of migraine. Specifically, we predicted that injecting an optogenetic virus stereotaxically into the PoT and stimulating the ipsilateral V1 region with light will induce light aversion.

## Methods

C57BL/6J mice each received an injection of a virus encoding channelrhodopsin 2 (ChR2) or a control vector) into the PoT, which selectively targeted efferent neurons in this region. This was immediately followed by implantation of a fiber optic cannula into layer 5 of V1. Six weeks following surgeries, behavioral assays were run to determine whether activation of the PoT and its cortical projections is sufficient for producing migraine-like symptoms. During these assays, mice received optogenetic stimulation of the visual cortex. The fiber optic cannulas were connected to a light source, which stimulated the target area with 5 ms, 20 Hz bursts every other minute. The primary behavioral assay was aversion to dim light as a surrogate of photophobia. For 30 minutes, mice moved freely inside a chamber where they could choose to spend time in the light half or dark half, while their movements and time spent in each side were recorded and later analyzed.

## Results

Overall, optogenetic stimulation of V1 did not produce a significant effect on light aversion between mice receiving an injection of the viral vector encoding ChR2 and mice receiving a control vector. However, the data did demonstrate a trend toward light aversion in the ChR2 mice. Interestingly, when evaluating data from only female mice, the ChR2 group did show significant light aversion compared to the control group.

## Discussion

This project indicates that projections from the PoT to V1 may be significant in inducing photophobia in the context of migraine, but current data cannot conclusively support the sufficiency of this claim. Because behavioral assays were conducted with a small number of subjects, repeating the experiment with a larger group of mice may provide more significant results. Further work with this cohort will include supplementary assays, such as hypersensitivity (von Frey assay), spontaneous pain (automated grimace assay), and anxiety (open field assay), which will provide a more robust measure of migraine-like symptoms. Additionally, Immunohistochemistry assays will also be conducted on these mice to confirm the precision of injection and optogenetic targeting.

**Impact of previous hip arthroscopy on outcomes of periacetabular osteotomy to treat hip dysplasia.**

Spencer Dempewolf, BS and Michael Willey, MD, University of Iowa Department of Orthopedics and Rehabilitation

**Background:** Hip dysplasia is defined by inadequate coverage of the femoral head by the acetabulum. It is often diagnosed in adolescence or early adulthood with functional limitations and pain that eventually lead to osteoarthritis. The severity of a dysplastic deformity is assessed with radiographic measurements. Disability is quantified with patient-reported outcomes (PROs). For patients with dysplasia as defined by a lateral center-edge angle (LCEA) of <20°, periacetabular osteotomy (PAO) provides a means of relief via reorientation of the acetabulum to provide improved coverage of the hip joint. For patients with borderline dysplasia (BHD), as defined by an LCEA 20°-25°, treatment with hip arthroscopy may be considered. There is significant controversy regarding the appropriate treatment of BHD. As high as 20% of hip arthroscopies fail in the treatment of BHD, leading many patients to seek PAO secondary to their previous hip arthroscopy.[1] The relative success of a secondary PAO surgery after failed arthroscopy has been studied in a limited capacity and with mixed results.

**Methods:** The Young Adult Hip team at the University of Iowa prospectively collects PROs and imaging measures on patients undergoing PAO preoperatively and 1-2-years postoperatively. The PRO survey obtains demographics, subjective hip function measures, and pain scores. The results of these surveys are used to calculate established hip function and pain interference scores, including the modified Harris Hip Score (mHHS) and International Hip Outcome Tool (iHOT). The present study included all patients that underwent first-sided PAO at UIHC between January 2018 and July 2021. Those with diagnoses other than hip dysplasia, previous hip surgeries other than arthroscopy, or concurrent surgical hip dislocation and femoral osteotomy were excluded. Parameters for measuring surgical success were established according to current literature as a postoperative mHHS ≥70, postoperative iHOT ≥63, and ΔiHOT ≥13.[2,3] Rates of revision surgeries were tracked in both groups, but the survey results from these patients were not used in calculations. Student's t-tests and regression analysis were performed for demographic variables, imaging measurements, and PRO scores, as appropriate. p-values less than 0.05 were considered significant.

**Results:** Preoperative and 1–2-year postoperative surveys were completed by 97 patients at the University of Iowa, with 82 of these having no history of previous hip arthroscopy and 15 with history of hip arthroscopy. There were no significant differences between demographics or hip function scores at baseline. Patients with no previous arthroscopy measured as having lower LCEA and higher Tönnis angle measurements at baseline than their counterparts (p=0.005 and 0.014, respectively), indicating that, on average, the group presented with more severe hip dysplasia. At 1-2-year follow-up, subjective hip function scores did not differ between the two groups regarding the mHHS (p=0.740), iHOT (p=0.755), or ΔiHOT (p=0.391). Additionally, the postoperative LCEA (p=0.819) and Tönnis Angle (p=0.203) were similar between the two groups. Percentage of patients achieving the surgical success measures of postoperative mHHS ≥70, postoperative iHOT ≥63, and ΔiHOT ≥13 was similar for each condition individually (p=0.407, 0.711, and 0.667, respectively). Two patients from the group without previous arthroscopy needed subsequent revision surgery, whereas no patients in the previous arthroscopy arm required revision surgery (p=0.153). Surgical success, as defined as meeting at least one of the three success parameters, was achieved in 94% of the entire group, 93% of the no previous arthroscopy group and 100% of the previous arthroscopy group (p=0.012).

**Discussion:** This study suggests that failed hip arthroscopy is not a risk factor for inferior secondary PAO outcomes within 1-2-years postoperatively at the University of Iowa. Both groups achieved clinically significant relief on average from their symptomatic hip dysplasia via the PAO procedure. The extent of relief, however, was similar based on hip function scores and imaging measures. The lower rate of patients with no previous arthroscopy meeting one of the three surgical success criteria was likely due to the higher percentage of severely dysplastic cases that comprise that group, but more study is needed to further delineate the rates of surgical success between the two groups. Limitations of the study include sample size, the limited range of postoperative timepoints, and that it is a single-center study. The present study can help guide course of treatment for borderline dysplastic patients, as this information can be used alongside known risk factors for inferior PAO outcomes such as age, BMI, and degree of osteoarthritis to aid physician counseling and patient decision-making. Future directions include continued patient data collection to increase sample size and expand follow-up into the 2-5-year postoperative range.

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**Title**
Depression in the time of COVID-19: Examination of prenatal and postpartum depression rates, rurality, and the impact of COVID-19

**Authors**
Ana M. DiSpirito, Mark K. Santillan, Stephen K. Hunter, Serena Gumusoglu, Julie Vignato, Elissa Faro, Heather A. Davis, Boyd Knosp, Donna A. Santillan

**Background**
Mental health conditions are a major contributor to many adverse perinatal conditions and cited as the cause for 7.0% of pregnancy-related deaths. However, despite the prevalence of these conditions, they are often underdiagnosed or misdiagnosed leading to delays in treatment. Many of the risk factors for depression are more prevalent in rural areas compared to urban areas, however, rurality is often not seen as a risk factor for developing prenatal or postpartum depression. Prevalence of prenatal depression has significantly increased since the beginning of the COVID-19 pandemic. This relationship between prenatal depression rates and prevalence of COVID-19 has been previously studied, but the literature examining this relationship in the context of urban-rural populations remains limited.

**Purpose of the study**
The purpose of this study was to investigate whether COVID-19 has had a significant effect on perinatal depression rates in the context of urban-rural populations and whether the COVID-19 pandemic has affected the incidence of depression in these populations receiving care at a large midwestern academic center. The results can be used to identify regions where women may be more at risk for depression and should be monitored and counseled regarding depression in more detail.

**Method**
We conducted a retrospective cohort study utilizing data selected from the Intergenerational Health Knowledgebase (IHK), a clinical research data warehouse that contains clinical and demographic data from pregnant women who received care at the Universities of Iowa Hospitals and Clinics (UIHC) from 2009-2021. EPDS and PHQ-9 questionnaires were used to assess rates of depression and Rural Urban Commuting Area (RUCA) codes were used to classify the status of women participating in the study as living in a rural (4-10) or urban (1-3) zip code. Additionally, to assess how COVID-19 may have impacted women during each trimester of their pregnancy, we examined data from a sub-cohort of women who completed COVID-19-related questionnaires during pregnancy.

**Results**
Before the COVID-19 pandemic, the risk of perinatal depression rates significantly increased for rural populations when surveyed with the EPDS (2.96% increase) and PHQ-9 (4.41% increase) questionnaires compared to urban populations. During the COVID-19 pandemic, the risk of perinatal depression remained increased for rural populations whether assessed with the EPDS (2.65% increase) or the PHQ-9 (3.45% increase) surveys compared to urban populations.

The EPDS questionnaire results showed a significant increase in depression rates after the COVID-19 pandemic started for rural (2.94% increase) and urban (3.24% increase) populations. In contrast, the PHQ-9 results showed a significant decrease in depression rates during COVID-19 for rural (4.16% decrease) and urban (3.20% decrease).

**Conclusion**
We found that living in a rural area is associated with a significantly greater risk for perinatal depression. This increased risk remained apparent whether evaluated before or during the COVID-19 pandemic. During the COVID-19 pandemic, prenatal rates of depression decreased but postpartum rates of depression increased.

**Title:** Dissecting the structural determinants of ANGPTL3-mediated inhibition of EL and LPL

**Authors:** Alex Dou, Sydney Walker, Rakshya Thapa, Bharat Bhattarai, Lucy Langmack, Kelli Sylvers-Davie, Brandon Davies

**Background:** Angiopoietin-like protein 3 (ANGPTL3) is a key regulator of lipid homeostasis and an emerging therapeutic target for the treatment of dyslipidemia and prevention of cardiovascular disease. Physiologically, ANGPTL3 is a homotrimeric protein that acts as a dual inhibitor of endothelial lipase (EL), an enzyme that hydrolyzes phospholipids of high-density lipoprotein (HDL) particles, and lipoprotein lipase (LPL), the primary enzyme responsible for hydrolyzing triglyceride-rich lipoproteins. As such, endogenous ANGPTL3 acts to elevate plasma triglyceride and HDL cholesterol levels. At present, however, the molecular mechanisms by which ANGPTL3 inhibits EL and LPL remain poorly understood, limiting the rational design of ANGPTL3-targeted therapies for dyslipidemia.

**Purpose:** This study aims to identify and characterize domains in ANGPTL3 that are required for inhibition of either LPL or EL using alanine-scanning mutagenesis, *in vitro* functional assays, and computational coevolutionary analysis.

**Methods:** Amino acid residues in the N-terminal coiled-coil domain (S17-R221) of mouse ANGPTL3 were mutated two at a time to alanine via site-directed mutagenesis. The resulting ANGPTL3 mutants were expressed via transient transfection of HEK 293T cells and tested for their ability to inhibit LPL and EL, form trimer complexes, and bind LPL and EL via fluorescence-based lipase activity assays, native polyacrylamide gel electrophoresis (PAGE), and NanoBiT split-luciferase binding assays, respectively. Coevolutionary statistical coupling analysis (SCA) of 509 ANGPTL3 protein sequences was performed to identify groups of coevolving residues, known as sectors, which may correspond to functional domains underlying ANGPTL3-mediated lipase inhibition and trimer formation.

**Results:** In the present study, a subset of 30 new ANGPTL3 mutants were generated and functionally characterized. Of these, 7 were found to exhibit significant defects in EL inhibition only, none were found to exhibit defects in LPL inhibition only, and 6 were found to exhibit defects in both EL and LPL inhibition relative to wild-type ANGPTL3. The remaining 17 mutants showed no defects in lipase inhibition. On native PAGE, 3 mutants showed reduced trimer formation, all of which were defective in EL but not LPL inhibition. Of the 13 mutants with defects in EL inhibition, none showed reduced binding affinity for EL. In contrast, 2 of 6 mutants with defects in LPL inhibition showed moderately reduced binding affinity for LPL.

In total, 93 of the 99 planned mutants have been successfully generated, and 71 have been characterized for changes in both EL and LPL inhibition: 15 showed defects in EL inhibition alone, 3 showed defects in LPL inhibition alone, and 17 showed defects in both EL and LPL inhibition. Of the 12 mutants which showed reduced trimer formation, all had defects in EL inhibition, and 8 had defects in EL inhibition alone, indicating that EL inhibition is likely dependent on trimer formation. In contrast, mutations that disrupted EL or LPL inhibition typically produced minimal changes in EL or LPL binding, respectively, suggesting that lipase binding and inhibition are mediated by different structural determinants in ANGPTL3.

Coevolutionary analysis of ANGPTL3 protein sequences identified two groups of coevolving residues, sector A and sector B, as candidate functional domains. Sector A localized to the previously defined N-terminal SE1 domain and was significantly enriched in residues implicated in both EL and LPL inhibition ($p<0.01$). In contrast, sector B localized to a yet uncharacterized region in the C-terminal coiled-coil domain which was significantly enriched in residues that specifically impact EL inhibition and trimer formation ($p<0.05$).

**Conclusions:** Mutations in ANGPTL3 that disrupt inhibition of both EL and LPL localize to the N-terminal SE1 domain, which corresponds to a group of coevolving residues which we define as sector A. In contrast, many of the mutations which produce defects specifically in EL inhibition were found to cluster within a novel group of coevolving residues in the C-terminal coiled-coil domain, which we define as sector B. Trimer formation was found to be critical for EL inhibition, whereas defects in lipase inhibition were not associated with defects in lipase binding. Together, these results suggest that general lipase inhibition and trimer-dependent EL inhibition are mediated by two distinct, coevolving domains in ANGPTL3. Future studies will aim to complete the functional characterization of the remaining ANGPTL3 mutants as well as identify candidate mutations of interest for physiological testing in mouse models.

**UI Med Research Days Abstract 2022**

# Sleeping Beauty as a Novel Screening Tool for Identifying Mechanisms of Venetoclax Resistance in Acute Myeloid Leukemia

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Venetoclax, a next generation BH3-mimetic and inhibitor of selective B-cell lymphoma-2 (BCL-2), has recently emerged as a promising therapy for patients with hematologic malignancies. First approved by the FDA for treatment of Chronic Lymphocytic Leukemia in 2016, Venetoclax recently received expanded approval for use in other leukemias such as AML—an acute form of myelogenous leukemia that has proven difficult to treat and achieve long-term remission rates in patients for several decades. While Venetoclax treatment can initially attain complete remission in nearly 40% of patients when used in conjugation with azacitidine, decitabine, or low-dose cytarabine, leukemic resistance has presented almost uniformly among AML patient populations in long-term clinical practice. As clinicians continually move towards wide-spread acceptance and use of Venetoclax therapy as a second or even third-line treatment, there is a dire need to understand and anticipate molecular mechanisms AML may utilize to circumvent treatment and cause patient relapse.

The Sleeping Beauty (SB) Transposon system is a novel tool that has recently empowered researchers to identify mechanisms of cancer progression and therapeutic resistance in various malignancies. Consisting of two core components—a Sleeping Beauty Transposase and mutagenic transposon—the SB mutagenic system offers a simple, inexpensive, and high-throughput method to identify key mechanisms of therapeutic resistance in cancers such as AML when paired with next generation sequencing technologies. In the present study, we describe a novel screening method to elucidate molecular mechanisms of Venetoclax resistance in Acute Myeloid Leukemia. Using Sleeping Beauty Mutagenesis through an *in vitro* approach, we aim to quickly and efficiently generate a catalog of candidate genes that may be altered or exploited by AML to resist pharmacologic therapy. Previous research suggests leukemia uses various strategies to subvert Venetoclax treatment. SB mutagenesis will generate a variety of resistant AML populations, likely including those that exhibit dysregulated expression of other BCL-2 family proteins such as MCL-1 and BCL-XL, mutations in BCL-2 and p53 pathways, and alterations in metabolism and oxidative phosphorylation—all alterations that previous work suggests is beneficial to AML under selection by Venetoclax. Ultimately, however, we expect and hope to identify alterations in cellular signaling pathways that have yet to be identified by other work, thereby providing a list of cellular targets that may be further explored as potential targets for precision-therapy in future AML patients.

**Title:** Associations between QCT textures and plasma biomarkers in COPD patients

**Collaborators:** Anthony El-Sokkary, Hira A. Awan M.B., Muhammad F. A. Chaudhary, Junfeng Guo Ph.D., Alejandro Comellas M.D., Eric A. Hoffman Ph.D., Joseph M. Reinhardt Ph.D.

**Background:** Chronic obstructive pulmonary disease (COPD) is a disease characterized by persistent respiratory symptoms and airflow obstruction, mostly as a result of chemical or environmental exposures. [1] According to data from 2018, 16.4 million or 6.6% of adults at the time reported a diagnosis of any type of COPD (chronic bronchitis, emphysema, or COPD) [2]. Currently, COPD prognosis is determined by indices like the BODE index which consolidate several known clinical measures including weight, forced expiratory volume in 1 second ($FEV_1$) [3]. Researchers involved in longitudinal, observational studies like the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) and Genetic Epidemiology of COPD (COPDGene) have been looking into quantitative computed tomography (QCT) based biomarkers as additional tools to improve prognostics and management of this complex disease. Previous work at Reinhardt lab by Chaudhary *et al*. demonstrated that CT-density gradient texture features are associated with exacerbation risk in participants from both the SPIROMICS and COPDGene cohorts. [4] As it was hypothesized that these texture features demonstrated areas of ongoing chronic inflammation, we wanted to further investigate underlying inflammatory mechanisms that might explain these radiologic patterns. In this study, we studied the associations between QCT textures and plasma-based biomarkers known to be associated with inflammation and COPD exacerbation risk from previous literature. [5]

**Methods:** Imaging data, clinical covariate data, and microarray plasma biomarker data for sRAGE, CRP, Alpha-2-Macroglobulin, Decorin, MMP-9 were collected from 963 participants from CODPGene and 1407 participants from SPIROMICS. Additionally, Microarray plasma data for IL-2, IL6, IL-8, Eotaxin (CCL11) were collected from those same 963 participants in COPDGene but gathered separately in a substudy from SPIROMICS yielding 892 participants. These plasma biomarkers were log-transformed for normality. Imaging biomarkers in our analysis included ground-glassing, honeycombing, and emphysema textures extracted using the adaptive multiple feature method (AMFM) [6]. These were accompanied by additional QCT biomarkers including Pi10, wall area %, density-based emphysema, and air trapping. Firstly, univariate regression analysis between imaging and plasma-based biomarkers was performed. Multivariable regression was then performed with the addition of BODE index, BMI, age, race, sex, bronchodilator response, post-bronchodilator FEV% of predicted, current smoker status, and pack-years as potential confounding features. Benjamini Hochberg correction was used to compute q-values in both the analyses to minimize false discovery rates. Finally, stepwise linear regression was performed as a method of feature selection to find combinations of imaging biomarkers for each plasma biomarker based on improved Akaike information criterion (AIC).

**Results:** In the SPIROMICS cohort, sRAGE was inversely correlated with density-based emphysema (b= -0.0112; q = 4.55e-17) and IL-6 was positively associated with ground-glassing texture (b = 0.00464; q =0.0165) and inversely with emphysema texture (b = -0.00229; q = 0.0122). In the COPDGene cohort, sRAGE was inversely correlated with density-based emphysema (b= -0.00332; q = 0.0101) and IL-6 was positively associated with ground-glassing texture (b = 0.00666; q = 0.00101) and inversely with emphysema texture (b = -0.00149; q = 0.00101). In the stepwise regression analysis density-based emphysema and ground-glassing texture were selected for sRAGE and ground-glassing texture was selected for IL-6. No other combinations of imaging biomarkers and plasma-based biomarkers were validated across the two cohorts. Other combinations of plasma-based biomarkers and QCT measures were not significantly associated across both cohorts.

**Discussion:** Our results reaffirm the findings by Pratt *et al.* which showed that sRAGE plasma concentrations were associated with density-based emphysema measures [7]. Furthermore, ground glassing texture was significantly associated with IL-6 across both cohorts in univariate, multivariable, and stepwise regression. We believe this texture pattern may demonstrate effects of systemic inflammation and may correspond with regions in the process of becoming emphysematous. In the future, we hope to explore whether these relationships hold true with the addition of longitudinal data. Further, the incorporation of genetic expression data into future analysis may provide greater insight into the mechanistic understanding of these relationships between QCT and plasma-based biomarkers.

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**Title:** Intracortical myelin differences among patients with Huntington's Disease
**Presentor:** Yumeng Engelking
**Mentor:** Timothy Koscik

**Background:**

Huntington's disease (HD) is a genetic, progressive, neurodegenerative disorder caused by huntingtin gene (Htt) polyglutamine (CAG) expansion and mutant huntingtin protein (mHtt) expression. Huntingtin protein is essential for neurodevelopment and neuronal migration in the cortex. The neurodevelopmental mechanisms of HD are not well established, and it remains unclear if failure of neuronal migration leads to persistent laminar structure abnormalities as HD progresses. Previous studies found morphological changes in cortical thickness. In preclinical, HD gene expanded individuals, thicker cortical gyri and thinner sulci have been observed. Our work studies the disruptions to cortical laminar structure in humans with HD. It will enhance our understanding of the neurodevelopment of HD.

**Purpose:**

We aim to catalog neuropathology in the laminar structure of the cerebral cortex in HD. We will investigate changes in cortical lamina using a proxy measure, intracortical myelin, that is quantifiable in vivo using magnetic resonance imaging. We will also study the relationships between the length of Htt CAG repeat elongation and variability in intracortical myelin.

**Methods:**

All neuroimages of cortical laminae were collected on 3T whole body scanner. T1- and T2-weighted images were processed using standard neuroimaging tools. Maps of intracortical myelin were generated by calculating the ratio of T1- to T2-weighted signal intensities. We compared intracortical myelin content between gene-expanded and non-gene-expanded individuals. Lastly, we examined the associations between intracortical myelin and CAG repeat expansion. We also examined the associations between intracortical myelin and cap score, which is a measure of the risk of developing HD symptoms in the near future, and calculated using cag and age. The higher the cap score, the higher chance of early HD onset. The data is analyzed in R software using linear regression mixed models.

**Results:**

228 gene-expanded individuals and 103 non-gene-expanded individuals were included. Among all participants, 152 individuals were male, and 179 individuals were female. We examined 56 regions across the cortex and found significant group differences in 10 regions including cerebellum, caudal, entorhinal, fusiform, occipital fusiform, insula, isthmus, parahippocampal, posterior insula, and precuneus. Compared to the non-gene-expanded individuals, the intracortical myelin content of gene-expanded individuals was significantly higher. Further analysis shows that both CAG repeats and cap scores have main effects on the intracortical myelin contents of the 10 regions. We discover that the intracortical myeline contents of the 10 regions increase as the cap score increases.

**Discussion:**

Our data shows that the intracortical myelin content in pre-clinical HD patients is higher than in healthy controls. This is consistent with previous evidence of regional increases in intracortical myelin in HD. The increased regional myelination content of the current study combined with thicker cortical gyri found in the previous study may indicate delayed neuronal migration, which leads to a higher concentration of myelination in specific locations. Among HD individuals, intracortical myelin differences are significantly impacted by both CAG repeat expansion and CAP score. It is reasonable to assume that older patients who have higher CAG repeats have higher intracortical myelination in specific regions across the cortex, which may contribute to the underlying neurodevelopmental mechanisms of HD. The interaction of CAG repeats and the risk of HD onset significantly impacted intracortical myelination difference, this combined effect may relate to both neurodevelopment differences and ongoing disease progression.

**Thin Film Zwitterionic Hydrogel Coating on Inner Surfaces of Tympanostomy Tubes Facilitates Mucus Discharge**

**Student: Caleb Escudero, M2**
**Mentor: Marlan R. Hansen, Otolaryngology--Head and Neck Surgery**

Background: The most common childhood surgery in the United States is placement of tympanostomy tubes with over 667,000 cases per year. These tubes are placed for children with recurrent cases of OM. Tympanostomy tubes allow ventilation and discharge of the infected middle ear, compensating for the poor function of developing eustachian tubes. Despite their frequent use, tympanostomy tubes suffer relatively high rates of complications. One major complication is obstruction of the lumen of the tympanostomy. Obstruction can result from mucus stasis, dehydrated conditions that dries outflowing mucus, and/or development of granulation tissue within the tube. Plugged tympanostomy tubes carry the risk of chronic OM, hearing loss, and further surgical intervention. A potential solution to this problem comes in the form of thin film zwitterionic hydrogels. Our lab has demonstrated that the hydrophilic properties of these thin films lead to a layer of hydration that is extremely versatile. The hydrogel has been shown to increase lubricity and reduce friction, which may prevent mucus stasis. The intensely hydrophilic nature of the hydrogel can prevent desiccating conditions within the tympanostomy tube due to it being more thermodynamically favorable for water to flow along the thin film through the tube, thus keeping mucus hydrated. Additionally, it has been previously demonstrated that the thin films exhibit anti-fouling properties that will prevent immune tissue formation and deposition. The purpose of this study was to determine how thin film zwitterionic hydrogel coatings on the inner surface of tympanostomy tubes would affect the dynamics of mucus discharge and obstruction.

Methods: Thin films were first photografted onto PDMS sheets using sulfobetaine methacrylate (SBMA), carboxylbetaine methacrylate (CBMA), or polyethylene methacrylate (PEGMA) as the principal monomer. Using mucus harvested from banana slugs, the sheets were used to test mucus contact angles, force required for mucus flow, and the effects of cross-link density. The thin films were then photografted onto the lumen of PDMS tubes. The tubes were used to test the amount of force required to discharge mucus from a tube, as well as the effect of the hydrogel on static mucus drying. Each of these variables was compared to uncoated PDMS as a control.

Results: Zwitterionic thin films (CBMA, SBMA, PEGMA) were shown to dramatically reduce the mucus contact angle, as well as the force required to initiate mucus flow relative to uncoated PDMS. All hydrogel types dramatically reduced the contact angle, though CBMA saw the largest reduction. Each hydrogel type was shown to reduce the force required to initiate flow on sheets, with no significant difference between hydrogel types. It was determined that mucus flowed most optimally between 10-25% cross-linker percentages. When testing SBMA-coated PDMS tubes, there was a significant reduction in force required to discharge the mucus through the tube. When testing drying rates of static mucus in vertical tubes, there was no significant difference found between the coated and uncoated groups.

Conclusions: The dramatic increase in mucus flow from the addition of thin film zwitterionic hydrogel coatings is likely attributed to its hydrophilic properties. As mucus is made predominately of water, it spreads itself to associate with the hydrogel, preventing a large and static blockage of the tube. While there was no difference between the time required to dry mucus that is statically filling a tube, the hydrogel significantly reduces the likelihood that those conditions would present. Coating of tympanostomy tubes with the thin films has a high potential to improve mucus flow and prevent stasis that would lead to plugging. Future projects include further testing of different hydrogel types in tubes, creating a more accurate model of mucus drying, and an *in vivo* study of coated tympanostomy tubes in rats.

**Can Topical Eyedrops Prevent Sympathetic Nerve Vasoconstriction of Ocular Vasculature?**

Riley Filister, BA, Randy Kardon, MD, PhD, Julie Nellis, RN, BSN

**Introduction:** Decreased blood flow resulting in optic ischemia has been implicated in vision loss in several conditions including glaucoma, diabetic maculopathy, and ischemic optic neuropathy. During physiological states of sleep, such as REM sleep, along with pathological sleep conditions, such as sleep apnea, bursts of sympathetic nerve activity have been recorded. We hypothesize that elevations in sympathetic nerve activity cause peripheral vasoconstriction, resulting in decreases in ocular perfusion. Given the potential role of sympathetic nerve bursts of activity in adversely reducing ocular blood flow to the retina and optic nerve, it is important to confirm this effect. We also set out to determine if treatment with brimonidine, a topical sympathetic blocker (alpha-2 agonist), and dorzolamide, a carbonic anhydrase inhibitor which is a direct-acting vasodilator, can mitigate sympathetically mediated increases in vascular resistance to the eye.

**Purpose:** Brimonidine (alpha 2 agonist) and dorzolamide (carbonic anhydrase inhibitor) are ophthalmic agents that have direct nervous modulation and direct vasodilatory effects, respectively. This research explores whether these topical eye drops may serve as agents to mitigate increases in vascular resistance due to sympathetic activation and, if so, whether this effect was limited to certain ocular vascular beds supplying the optic nerve head, choroid, or retina.

**Methods:** Ten healthy subjects (age range 50-80) who had previously served as untreated controls for ice water-induced vasoconstriction were re-evaluated to determine if pretreatment with topical agents to one eye mitigated sympathetically induced vasoconstriction. Participants self-administered one drop of brimonidine 0.2% TID to a single eye for 3 days prior to testing. On test day, participants' intraocular pressures (IOPs) were measured, and continuous measurements of peripheral arterial tone (PAT) amplitude of both index fingers were collected using a WatchPAT 300 device (Itamar Corp.) Participants then submerged the foot ipsilateral to the brimonidine-treated eye into ice water for 2 minutes. Blood pressure measurements using an automated blood pressure device and blood flow measurements to both eyes using laser speckle flowgraphy (LSFG; Softcare LTD) were recorded prior to foot immersion, during immersion, and at two- and 10-minutes post-immersion. Following a one-week washout period, this protocol was repeated on the same eye using topical dorzolamide (20 mg/mL).

**Results:** Repeated-measures ANOVA in the control condition demonstrated a significant increase in vascular resistance during ice water immersion compared to at baseline in the ONH and PPC. Repeated-measures ANOVA demonstrated an increase in retinal vascular resistance between baseline and cold water immersion in brimonidine-treated eyes, with no difference in vascular resistance between baseline and cold water immersion in other brimonidine-treated vascular beds or any dorzolamide-treated vascular bed. Paired t-tests showed no significant difference in percent change in blood flow or vascular resistance between baseline and ice water immersion was seen between the treated and untreated eyes for brimonidine or dorzolamide, save for a significant decrease in blood flow and increase in vascular resistance in the brimonidine-treated choroidal vessels.

**Conclusions:** Based on these results, an increase in ocular vascular resistance induced by cold water immersion does not appear to be due to a direct sympathetic nerve effect on the distal end-arteries of the retina, choroid, or optic nerve head. One possibility is that an increase in ocular peripheral vascular resistance may be due to an autoregulatory vasoconstrictor response caused by cold water-induced high blood pressure. Topical dorzolamide, through its direct vasodilatory effects, appears to reduce this effect. Future studies will investigate means of directly increasing sympathetic nerve activity to the eye's vasculature during the awake state when ocular blood flow can be measured.

**Project Title:** Artificial Intelligence to Determine the Age of a Hand
**Student:** Madeline Fitzhugh, M2
**Mentor:** Dr. Jennifer G. Powers, MD
**Collaborators:** Dr. Kevin Chu, PhD; Ananya Munjal, MS, BS; Nora Bensellam, BA; April Zhang

## Introduction
Current enthusiasm for AI applications in Dermatology has been mostly about improving detection of skin cancers. Characterizing aging is an important process for health and aesthetic reasons, but no AI study has yet sought to predict age based specifically on dermatological signs of aging such as reduced laxity, skin thickness, wrinkles, photoaging, irregular pigmentation, telangiectasias (dilated blood vessels), and areas of purpura (purple-colored spots due to leaking blood vessels). Previous age prediction research has combined facial landmarks, facial feature points, and texture features to improve age prediction with facial images. While many technologies exist under the umbrella term "AI", Deep Learning is the presiding AI technology for analyzing complex data such as images. DL uses unstructured data in its raw form, such as text or images, to determine the set of distinguishing features. Studying hands provides an often forgotten aesthetic skin unit to best represent natural aging processes, as well as a unique opportunity to study aging as it relates to vehicle associated sun exposure, possible occupational exposures, and handedness in daily activity.

## Hypothesis
We aim to create an AI algorithm that will be able to accurately predict an adult patient's age within +/- 5 years from visual patterns of hand photographs in a controlled environment, across skin types and age ranges.

## Methods
Participants were sourced from UIHC Dermatology Clinic, MERF, and Wesley Life The Village retirement home. Exclusion criteria include history of dermal hand filler, hand tattoos, and inability to remove hand/wrist jewelry, which preserves anonymity and aid in standardization of photographs. Participants were given a REDcap survey gathering birth year, gender, race/ethnicity, handedness, occupation, daily hand sunscreen SPF 30, average daily driving, average daily sun exposure, and the geographic region they have spent the most time. Photographs were standardized using a photography box with attached LED ring light and a green background to control for lighting differences, and distance from target. The dorsal aspect of each hand was photographed separately in a relaxed position using an iPhone square lens 1x setting with absence of any filters.

## Results
Data collection measures have sourced 149 records, with a distribution of 65 (43.6%) male and 84 (56.4%) female participants. The average participant age is 53 years old. 125 (83%) of participants are Caucasian/White. Healthcare/Medical is the predominating occupation with 54 (36.2%) participants. Handedness of the participant population reflects that of the general population, approx. 90% right, 10% left. Regional distribution is skewed towards Midwest with 110 (73.8%) of participants.

## Discussion
This preliminary project will be continued to collect sufficient data to accurately run the algorithm to draw conclusions on its success. Caretaking/Stay at Home Parent, Student, and

**Association between degree of physical activity and the presence of pelvic floor disorders in a cohort of parous Ugandan women**

Student Author: Julia Fleecs
Mentors: Dr. Kimberly Kenne and Dr. Brooks Jackson
Collaborators: Dr Micheal Derrick Ngobi, Dr Flavia Matovu Kiweewa, JaNiese Jensen, Ramya Vemulapalli, Linder Wendt

**Background:** Pelvic floor disorders (PFD) including urinary incontinence (UI), anal incontinence (AI), and pelvic organ prolapse (POP), affect women worldwide and can have a devastating impact on quality of life. In low- and mid-income countries (LMIC) research regarding PFD remains scarce, despite women in these areas having the potential to be at a higher risk for the disorders. Women in LMIC often have more pregnancies, poor nutrition, more physical demands in daily life, and less access to obstetric and gynecologic care. These factors may increase the negative impact PFD have on quality of life. The presence of PFD is generally determined by symptom assessment, standardized questionnaires, and a standardized physical exam. To improve access to quality-of-life treatment in Uganda, a knowledge of prevalence and risk factors is necessary, specifically the factor of physical activity.
**Aim:** The objective of this study was to assess the association between degree of physical activity and presence of pelvic floor disorders in parous Uganda women.
**Methods:** We conducted a prospective cohort study at Makerere University- John Hopkins University (MU-JHU) Research Collaboration in Kampala, Uganda examining PFD in parous women. Participants enrolled in the Maternal Repeat Pregnancy Bone Health Study (MBHS) were offered co-enrollment in the PFD study. The presence of PFD was measured in three ways; a symptom assessment, standardized questionnaires (Pelvic Floor Distress Inventory (PFDI-20) and Pelvic Floor Impact Questionnaire (PFIQ-7)), and a standardized physical exam (pelvic organ prolapse quantification (POP-Q) exam and a cough stress test (CST)). The degree of physical activity was assessed using a MBHS questionnaire which highlighted activity related to occupation, travel, and leisure. Socio-demographic data were obtained from patient interview and patient medical records. Institutional Review Board approval was obtained through University of Iowa and MU-JHU. Continuous variables were summarized using medians and inter-quartile ranges (IQR), while categorical variables were summarized using counts and percentages. To examine the association between minutes of exercise and PFD, a log transformation was applied to the weekly minutes of exercise variable and a logistic regression model was constructed with weekly minutes of moderate/vigorous exercise, age, BMI, and parity as the predictors.
**Results:** 111 women were enrolled as of August 22, 2022 with a median age of 35 (IQR 32 – 38), median parity of 4 (IQR 3 – 5), and median BMI of 29 (IQR 24 – 33). The prevalence of PFD as determined by symptom assessment is 31%. The most common stage of prolapse as determined by POP-Q was stage II (53%). 55 (50%) women had a positive CST with a median bladder volume of 145 mL. 47 (42%) of the women report vigorous physical activity, with a median level of 441(IQR 180-900) minutes/week. 100% of the cohort reports moderate physical activity, with a median value of 1,500 (IQR 1,050 – 1,978) minutes/week. 91 women (82%) in the cohort report traveling by bike or walking, with a median value of 30 (IQR 30 – 45) minutes/week. When controlling for age, parity, and BMI there is a significant association between the presence of PFD based on standardized physical exam (POP-Q) and vigorous physical activity level (doubling one's vigorous physical exercise corresponds to a 9% increase in their odds of POP $p = 0.048$). Moderate physical activity was not found to be associated with presence of PFD after controlling for age, parity, and BMI ($p = 0.7$).
**Conclusions/Discussion:** PFD as determined by standardized physical exam are common among parous Ugandan women and are associated with vigorous physical activity.

Title: DEVELOPMENT OF THE IDEAL PEDIATRIC AIRWAY EMERGENCY CART: STANDARDIZATION, STREAMLINING, AND SIMULATION

Authors: Fleishhacker ZJ, Bennion DM, Kanotra S

Introduction: The emergency pediatric airway can be among the most tenuous scenarios faced by on-call providers, requiring a timely response and quick access to appropriate equipment. This quality improvement project sought to provide recommendations for improving our institution's existing pediatric emergency airway carts and to also evaluate response times and resident confidence in responding to acute airway emergencies using simulated situations.

Methods: Several cart configurations were considered, including video tower and bronchoscope on separate cart or on the same cart containing all other emergency airway equipment. Volunteer Otolaryngology resident physicians were tasked with responding to a mock pediatric emergency airway scenario in the PICU with either the updated cart or the existing cart. Outcomes included 1) time to resident arriving at the bedside with all appropriate equipment, 2) time from arrival with all appropriate equipment to complete assembly of video capable flexible bronchoscope & rigid laryngoscope, and 3) time for re-assembly after initial attempt.

Results: Updating existing pediatric emergency airway carts to include a flexible bronchoscope and a video tower resulted in improved times to arrival with necessary equipment to the patient bedside. Increased resident familiarity equipment improved assembly time in a mock emergency airway scenario.

Conclusion: The results of this QI project support standardization of pediatric emergency airway cart equipment, with emphasis on inclusion of flexible bronchoscope and video endoscopy and simulation for team members to gain familiarity with emergency airway equipment. Streamlining of the pediatric emergency airway equipment improves efficiency, which can serve as an argument for allocating institutional resources to updating the carts to maximize the chance of favorable outcomes in these high stakes emergency airway scenarios. Simulation of patient scenarios lead to improved confidence and lesser reaction time. Future studies in actual clinical scenarios will be helpful to confirm the effectiveness of this approach.

# Distal Biceps Tendon Reconstruction with Achilles Tendon Allograft: A Case-Series

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**Abstract:**

**Background:** Chronic, complete ruptures of the distal biceps tendon are often difficult to surgically repair due to significant fibrosis and retraction. The use of a graft is recommended, with recent literature suggesting that an Achilles tendon allograft leads to superior clinical outcomes. The purpose of this study is to present the surgical technique and retrospectively review the clinical outcomes of a distal biceps reconstruction technique that utilizes an Achilles tendon allograft and with an Endobutton bicortical fixation system through a single S-shaped incision.

**Methods:** Seven male patients and eight cases of distal biceps reconstruction with Achilles tendon allograft were identified between January 2017 and March 2022. The mean age was 48.3 ± 8.9 years with a mean time from initial injury to surgery of 6.1 ± 3.8 months. Charts were retrospectively reviewed for patient demographics, procedural technique, preoperative and postoperative evaluation, and complications.

**Results:** The cohort had a mean follow-up of 4.6 ± 2.0 months (range, 1.4-8.2). At the final office visit, full range of motion had returned for all patients except one, who had a persistent 10° extension deficit. Flexion strength had returned to equal preoperative and preinjury gross strength out of 5 (4.7 ± 0.5 preoperatively versus 4.4 ± 0.5 postoperatively, p=0.37) and supination improved from preoperative strength (2.2 ± 1.1 preoperatively versus 3.6 ± 1.2 postoperatively, p=0.02). Four out of eight cases resulted in a new neuropraxia identified in postoperative care: two lateral antebrachial cutaneous nerve, one superficial branch of radial nerve, and one ulnar nerve, with insufficient follow-up duration to determine resolution. One patient reported excessive scar formation, otherwise, there were no major complications.

**Conclusions:** Reconstruction of the distal biceps tendon using an Achilles tendon allograft is a technically challenging, yet effective approach for the treatment of complete distal biceps tendon ruptures that are chronic in nature, resulting in an improvement in preoperative disability with few postoperative complications.

**Level of evidence:** IV – Case Series

**Keywords:** Distal Biceps; Reconstruction; Achilles Tendon Allograft; Distal Biceps Tendon Rupture

**A Nationwide Emergency Department Data Analysis to Evaluate Health Disparities in High-Risk Medication Use Among Older Adults**

Student: Gabrielle Frediani
Mentor: Sangil Lee
Collaborators: Uche Okoro and Ryan Carnahan

**Background:** High-risk medications are potentially harmful medications, which include benzodiazepines, barbiturates, prescription anticholinergics, and non-benzodiazepine hypnotics (Z-drugs). Older adults are at risk for adverse events due to high-risk medications, so identification of high-risk medications and deprescribing during hospital stays is a high-yield area for intervention.

**Purpose:** The objective of this study was to evaluate the rural versus urban disparity in the pattern of high-risk medication prescription and administration for older adults during emergency department (ED) visits in the United States. Additionally, we aimed to evaluate the mediation effect of dementia diagnosis on the rural vs. urban status and use of high-risk medications related to emergency departments in the United States. We hypothesized that the prescription or administration of high-risk medications is more common in rural EDs than in urban EDs in the United States, and the association between rurality and the prescription or administration of high-risk medication is mediated by the presence of dementia compared to other conditions seen in EDs.

**Methods:** This study examined data from the National Hospital Ambulatory Care Survey (NHAMCS). We extracted older adults (age 65 or greater) who were treated in the ED in 2019 from the NHAMCS, excluding federal, military, and Veterans Administration hospitals in the 50 US states and the District of Columbia. We used metropolitan statistical area (MSA) versus non-MSA status to define the rurality of where EDs are located. We defined the outcome as the prescription or administration of any high-risk medications listed under the American Geriatrics Society (AGS) 2019 Beers Criteria as a medication that is potentially inappropriate in most older adults. A multivariable logistic regression model was created to assess demographic, clinical, and hospital factors associated with high-risk medication prescription.

**Results:** We identified a total of 27,748,006 observations in the 2019 dataset. 1,760,370 (95% CI 1382484 - 2138255, 6.34%) of these observations had dementia. A total of 6,826,135 (95% CI 5647230 - 8005040, 24.6%) observations received any type of high-risk medications in the ED in 2019. People with dementia had higher odds of being prescribed or administered high-risk medications (OR 1.560, 95% CI 1.103 - 2.207). No difference was observed in the odds of being prescribed or administered high-risk medications in rural compared to urban EDs in 2019 (OR 1.027, 95% CI 0.694 -1.520).

**Conclusion:** A disparity in the prescription or administration of high-risk medications in rural compared to urban areas was not observed for older adults seen in United States EDs. However, a diagnosis of dementia was associated with increased odds of receiving high-risk medications. These findings indicate a further need to evaluate the quality of medication prescribing for older adults with dementia in the ED.

**A Case of Idiopathic Plastic Bronchitis in an Adult Post-Lung Transplantation**

**Authors:** Garrick Gama, BS1, Michelle Bremer, BS1, Eugene Golts MD2, Kamyar Afshar, DO2

**Background:** Plastic bronchitis is a rare, potentially life-threatening condition characterized by casts formed within the tracheobronchial tree leading to partial or complete airway obstruction. Pathogenesis is unclear, but it has been described in various non-transplant settings. This case report documents plastic bronchitis in a lung transplant recipient several months following lung transplantation -- a finding sparsely covered in the literature to date. Plastic bronchitis leads to increased hospitalizations and mortality in non-transplant populations, however, data regarding recurrence rates and prognosis in lung transplant populations are difficult to assess based on the lack of current documentation.

**Case Report:** A 75-year-old man underwent a right single LTx for Idiopathic Pulmonary Fibrosis (IPF) without any primary graft dysfunction. Transplant course was complicated by spontaneous R hemothorax 1-week post-LTx which was successfully treated. He was discharged from hospital 2 weeks post-LTx. Five months following LTx, he complained of a rapidly progressive dyspnea on exertion, non-productive cough and hypoxemia. Chest CT imaging showed perihilar consolidation and peribronchovascular consolidative opacities in all lobes of the right lung. Initial diagnostic work up for infections and biopsies were all negative. His symptoms continued to worsen over a 2-week period requiring intubation and mechanical ventilation with FiO2 as high as 100% and positive end-expiratory pressure (PEEP) of 10 to maintain adequate oxygenation. Repeat bronchoscopy noted thick, white secretions and casts partially or completely occluding the RUL, RML and RLL. Suction was applied and forceps were used to remove the thick, adherent white casts. Pathology noted bland appearing acellular casts. Inhaled N-acetylcysteine (NAC), pulmozyme, and hypertonic saline were administered in addition to the repeated daily therapeutic suction and forceps removal of the casts to allow for airway patency, totaling 12 bronchoscopies over a 2-week course. His situation gradually improved and was liberated from the mechanical ventilator and reduced oxygen requirement.

**Discussion:** Given the rarity of this complication following lung transplantation, recurrence rates and overall prognosis are difficult to ascertain. Contrary to prior reported cases, our post-LTx case of plastic bronchitis presented 5 months following lung transplantation in a progressive fashion. This was outside the early post-LTx phase that would relate to surgery or lymphatic disruption. Casts were thick and white grossly with acellular histologic findings, suggesting Type II plastic bronchitis. Although rare, further studies should be performed to better understand the pathology and risks of developing plastic bronchitis.

**Metastatic Disease to a Concurrent Thyroid Neoplasm: A Case Series and Review of the Literature**

Student: Michael Garneau
Mentor: Geeta Lal, Surgery

Metastatic disease to the thyroid gland is uncommon but well-described. Metastatic disease to a concurrent primary thyroid neoplasm is a rare phenomenon. We report a series of patients with metastatic disease to the thyroid, with or without a concurrent primary neoplasm. Four patients developed papillary thyroid cancer, with metastatic spread of a different malignancy seeding into the thyroid cancer. The diagnostic process, clinical management, and overall course of tumor-to-tumor metastasis in the thyroid is included and the unique histopathologic features are discussed. We provide the largest-to-date and comprehensive review of the literature to identify all previous reported instances of tumor-to-tumor metastasis involving the thyroid.

**Defining Pulmonary Ionocyte Biology using the FOXI1-KO Ferret Model**

Grace Gasser*, Feng Yuan*, Yan Zhang, Idil Evans, Xingshen Sun, Nan He, Miao Yu, Bo Liang, and John F. Engelhardt

*Equal Contribution

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Recently identified FOXI1 expressing pulmonary ionocytes express higher levels of CFTR than other airway cell types. These poorly characterized and rare ionocytes may participate in airway epithelial ion transport and fluid balance, and thus could be important targets for gene therapy of cystic fibrosis (CF) lung disease. The *Foxi1* gene is essential for the specification and development of ionocytes, and its elimination in mouse tracheal epithelium causes decreased *Cftr* expression, increased effective viscosity of airway mucus and increased ciliary beat frequency. However, *Foxi1* knockout (KO) mouse airway epithelia produced compensatory "*Cftr*-like" currents, and CF mice do not spontaneously develop lung disease like CF patients. To address these challenges we generated *FOXI1*-KO ferrets using CRISPR/Cas9-mediated gene editing in zygotes to test the hypothesis that ionocyte ablation within airway epithelium will lead to alterations in airway epithelial ion transport and CF-like lung disease. Two sgRNAs targeting exon-1 of the *FOXI1* gene with the highest *in vitro* cleavage efficiency were injected into ferret zygotes with Cas9 protein. CRISPR/Cas9 induced indels at the *FOXI1* locus in founder ferrets were detected by PCR, Sanger sequencing, and Tracking of Indels by Decomposition (TIDE) analysis. We generated 3 heterozygous or chimeric *FOXI1*-KO founder ferrets with 5 unique insertion/deletions (indels). All indels produced frameshift mutations resulting in premature stop codons, which are predicted to produce a complete loss of protein function. *FOXI1*-KO ferrets were generated through the breeding founder ferrets. The offspring were genotyped by Sanger sequencing and TIDE analysis, and tissue samples were characterized for FOXI1 protein and mRNA levels by Western blot and RT-PCR, respectively. FOXI1 protein expression in the kidney was absent by Western blot and FOXI1 mRNA was significantly reduced. All *FOXI-KO* ferret kidneys exhibited an absence of the intercalated cell markers pendrin and AE1 by mRNA expression, consistent with *FOXI1* being required for specification of intercalated cells in the distal renal tubular epithelium. Polarized *FOXI1*-KO airway cultures demonstrate CFTR-mediated chloride and bicarbonate currents that are both significantly decreased compared to WT. These same cultures showed a 50% decrease in CFTR expression when measured by qPCR analysis without showing an appreciable change in transcripts marking secretory and ciliated cells (*MUC5B, MUC5AC, FOXIJ1*). Polarized *FOXI1-KO* and WT airway cultures also demonstrated significantly altered airway surface liquid properties including a decreased ASL height and impaired alkalinization response to forskolin-IBMX stimulation. This data shows that the *FOXI1*-KO ferret model may be useful in elucidating the multi-functional and physiological roles of pulmonary ionocytes in airway diseases.

**Title**: Retrospective cohort study of patients with multiple days fully awake in the intensive care unit shows that far fewer than half the patients had follow-up assessment for post-intensive care unit syndrome

**Student:** Brian Gu
**Mentors:** Rachel Hadler, MD (Primary) and Franklin Dexter, MD PhD (Co-Investigator)

**Background:** Physicians and nurses at the University of Iowa treat many of the critically ill patients in Iowa. Many (>20%) patients surviving critical illness develop post-intensive care syndrome (PICS), a constellation of psychological, physical and cognitive symptoms which can have long-term consequences. Patients awake for long (>48-hour) periods in intensive care units often experience severe distress.

**Purpose:** Estimate the percentage of patients discharged alive who have follow-up assessment for PICS.

**Methods:** The University of Iowa Institutional Review Board determined that the retrospective cohort study was exempt from written informed consent. Adult patients were selected at random from an existing database of patients continually awake in the surgical or cardiovascular intensive care unit between October 1, 2014 (when electronic health record data was complete) and December 31, 2020. Patients were selected for review if their Riker sedation-agitation scale was equal to 4 (calm and cooperative) and either Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) negative or the Delirium Observation Screening Scale (DOSS) < 3. Manual chart review was performed using Epic electronic health records, treated as complete if there was an encounter at the University of Iowa at least 12-months but no greater than 15-months after the last date awake in an intensive care unit. Major comorbidities were recorded as defined by the Centers for Medicare and Medicaid Services codes. District of patient's home residence was recorded as defined by the Iowa Hospital Association. An initial sample of 53 patients was collected at random, with 5.66% (3/53) incidence of assessment. Patients were then selected at random until there were 73 with complete follow-up, 73 providing 90% statistical power to detect two-sided difference with Type I error rate of 0.01 between 20% and the estimate of 5.66%.

**Results:** There were **21% (15/73)** patients assessed for PICS sequelae during follow-up (**99% confidence interval 10% to 35%**). There were 10 assessments of mood (4 at cardiac rehabilitation, 5 at behavioral health visits, and 1 at family medicine visit) and 9 of cognitive function (4 at behavioral health visits, 2 at neurology, 2 at neurosurgery, and 1 at neuropsychology). Among patients receiving follow-up, 12% (N=9) developed delirium during the remainder of their hospitalization. Demographics included 44% (N=32) female, 47% (N=34) from the hospital's health district, 52% (N=38) with major comorbidities, 84% (N=61) with Medicare or Medicaid insurance, and 97% (N=71) white.

Among the 366 patient records screened to obtain 73 patients, 46 of the 366 did not meet inclusion criteria (e.g., satisfied CAM-ICU awake and alert, but DOSS positive for slow reactions and dozing off easily). The remaining 247 patients (366-73-46) lacking full follow-up included 27% (66/247) who died during hospitalization or within 12 months post-discharge. Thus, fewer, 12% (30/247), were assessed for PICS sequelae versus patients with full follow-up, showing validity. Demographics included 42% (N=104) female, 42% (N=103) from the hospital's health district, 47% (N=116) with major comorbidities, 77% (N=191) with Medicare or Medicaid, and 87% (N=215) white. There were no (0%) assessments for post-traumatic stress disorder (0/366). The initial 5.66%, above, from the first 53 records was similar to the ratio of assessments of the subsequent patients, 10% (30/ [366-53]), showing reliability.

**Discussion:** Rates of assessment for PICS sequelae were low, showing that sequelae were not being prioritized in routine follow-up appointments post-hospitalization, particularly within the first 12 months. Retrospective cohort studies of University of Iowa data cannot be used to judge incidence of PICS. On the other hand, the demographic variables were comparable between patients with and without follow-up suggesting that case-control analyses could be performed while limiting consideration to patients with complete follow-up. Further study is needed to assess methods for improving PICU screening.

The ≈12% delirium rate in awake patients was relatively low. The finding suggests that awake ICU patients can be screened and treated for distress with acceptable recall and low dropout rates.

**Sodium-Glucose Cotransporter-1 in Diabetic Cardiomyopathy**

Lina Gu, Dr. Ferhaan Ahmad

## Introduction

In diabetic cardiomyopathy, patients with diabetes mellitus experience a cardiomyopathy independent of other risk factors, such as hypertension or coronary artery disease. This cardiomyopathy leads to impaired diastolic and systolic cardiac function, that ultimately increases the risk of heart failure. The pathophysiology behind diabetic cardiomyopathy is complex, and changes in glucose transport have been shown to play significant roles. Cardiac function relies heavily on glucose uptake, mainly through the GLUT1 and GLUT4 transporters. However, the Ahmad lab has discovered that the sodium-dependent glucose cotransporter-1 (SLGT1) is also highly expressed in the heart, specifically in cardiomyocytes. Although GLUT1 and GLUT4 have been studied extensively in the context of diabetic cardiomyopathy, the role of SLGT1 is much less understood. SGLT1 transports glucose against its concentration gradient into the cell, using the $Na^+$ gradient established by the $Na^+/K^+$-ATPase pump. We have shown that SGLT1 expression is increased in diabetic cardiomyopathy, and SGLT1 knockdown is able to attenuate pathological processes associated with diabetic cardiomyopathy, such as mitochondrial dysfunction and apoptosis. Thus, SGLT1 may have value as a therapeutic target for treatment of diabetic cardiomyopathy.

## Purpose

This study aims to uncover the mechanisms by which SGLT1 inhibition attenuates diabetic cardiomyopathy. We hypothesize that in diabetic cardiomyopathy, hyperglycemia and hyperinsulinemia increase activation of ERK, which increases binding of the HNF-1 and Sp1 transcription factors to the SGLT1 gene promoter. The increase in SGLT1 expression then activates Nox2 signaling pathways, which lead to increased production of reactive oxygen species and the cardiomyocyte injury and dysfunction associated with diabetic cardiomyopathy.

## Methods

Immunoblots of ERK and Nox2 were conducted on cardiac tissue proteins collected from wild-type mice and transgenic mice with cardiomyocyte-specific RNA interference knockdown of SGLT1. These mice were given either a high-fat diet to simulate diabetes mellitus type II or a control diet.

## Results

In both the wild-type mice and the SGLT1 knockdown mice, high-fat diet increased both the active (phosphorylated) and total ERK protein levels. There was no difference in the ERK expression in the wild-type mice compared to the SGLT1 knockdown mice. We also observed no differences in Nox2 protein expression, when comparing control and high-fat diets in wild-type mice and SGLT1 knockdown mice.

## Discussion

These results support our hypothesis that ERK signaling is activated by diabetes and is unaffected by SGLT1 knockdown because SGLT1 is downstream of ERK in the signaling cascade. However, these results were not consistent with our hypothesis that SGLT1 regulates Nox2 expression. We may have been statistically underpowered to detect differences among the groups. Therefore, in future studies, we will quantify Nox2 protein expression in more mice, as well as expression of additional proteins hypothesized to be involved in SGLT1 regulation and signaling, such as the transcription factors HNF-1 and Sp1. Once the mechanisms by which SGLT1 contributes to diabetic cardiomyopathy are elucidated, specific therapies targeting the SGLT1 pathway can be developed for diabetic cardiomyopathy.

# The impact of alcohol sales in a college football stadium on healthcare utilization

Christopher Halbur, BS, David Ruehlmann, MD, Cassandra Moylan, MD, Peter Georgakakos, DO, Matthew Negaard, MD, Hans House, MD

**Background**
In 2021, for the first time, alcoholic beverages were available for purchase by adults attending a home college football game at Kinnick stadium in Iowa City, IA. This stadium routinely hosts >65,000 spectators and drinking is highly prevalent at pre-game tailgating events. The aim of this study was to determine the impact of this policy change on the local healthcare and emergency medical services (EMS) systems. We hypothesized that the wider availability of alcohol inside the stadium would lead to an increase in patients seen for alcohol-related complaints.

**Methods**
This was a retrospective study including patients who presented to the ED or to local EMS on Saturdays with a football game during the 2019 and 2021 seasons. The 2020 season was excluded due to the impact of COVID-19 on attendance. Trained extractors, using pre-defined criteria, reviewed patient records to determine if each visit was alcohol-related. The odds of an ED visit or EMS call being alcohol-related before and after the start of stadium alcohol sales were compared using logistic regression analysis. A multivariable logistic regression model was used to adjust for covariates between the two seasons, including patient age, sex, and kickoff times. Characteristics of visits before and after the onset of stadium alcohol sales were compared using a student's t-test for continuous variables, a chi-square test for categorical variables, and a Mann-Whitney U test for ordinal variables.

**Results**
Local emergency medical services received 16.6 alcohol-related calls per home game in 2019 and 12.7 per home game in 2021, when alcohol was sold in-stadium (p=0.34). There were more calls (505) in total during 2021 but fewer were alcohol-related (29%) (p=0.03). With in-stadium alcohol sales, the odds that an EMS call on a game day was alcohol-related was decreased (OR=0.73; 95% CI: 0.54-0.98). However, this difference was no longer significant after adjusting for covariates (aOR=0.83, 95% CI: 0.48-1.42). There was no difference in age, sex, or blood ETOH level between alcohol-related calls in each season (all p>0.2). Factors associated with increased odds of a call being alcohol-related included age 18-30, male sex, evening kickoff time, presence of physical injuries, and transport origin from a dormitory, bar/restaurant, or from the football stadium.

There were 13.9 alcohol-related emergency department visits per home game before stadium alcohol sales and 10.3 per game when the stadium sold alcohol (p=0.23). 1414 patients were seen on game days in 2021, with 8% of them presenting for alcohol-related reasons; similar to 2019, when 9% of 1538 patients presented due to alcohol (p=0.31). After adjustment for covariates, there was no difference in the odds of an ED visit being alcohol-related following the onset of stadium alcohol sales (aOR=0.98, 95% CI: 0.70-1.38). There was a reduction in the rate of alcohol-related ED visits within the 6 hours following kickoff in 2021 (6.7%) compared to 2019 (13.0%) (OR=0.55, 95% CI: 0.32-0.97). Factors that were associated with greater odds of an ED visit being alcohol-related included ages 18-30, male sex, highest acuity level, ED arrival later in the day, arrival in police custody, and leaving AMA/eloping.

**Conclusion**
The onset of alcohol sales within a large college football stadium did not increase the frequency of alcohol-related ED visits or local EMS calls. In fact, there were decreases in alcohol-related patient presentations within 6 hours following kickoff. The reason for this is unclear, but it is possible that fans drank less at tailgate parties knowing they could consume more once the game started. Long lines and a two-beverage limit at stadium concessions may have kept patrons from consuming excessively. The results of this study may inform similar institutions for the safe implementation of alcohol sales during mass-gathering events.

**Title:** Development of a Portable, Automated Evaluation of Ocular Misalignment
**Name and collaborators:** Emma Hartness, BS; Julie Nellis, BSN; Alex Kiderman, PhD; Yakov Eydelman, MS; Randy Kardon, MD, PhD (mentor); Alina Dumitrescu, MD (PI)

**Introduction:** Misalignment of the eyes can occur from a variety of causes, resulting in double vision, which adversely affects employment and quality of life. Ocular misalignment (strabismus) can be treated optically with prisms or surgically to achieve single binocular vision. Double vision requires extensive clinical evaluation to determine the pattern corresponding to conditions such as eye muscle imbalance by measuring the horizontal and vertical misalignment in different fields of gaze. This information helps localize the site of damage and its cause (e.g. extra-ocular muscle, neuromuscular junction, cranial nerve) in order to plan treatment. This evaluation currently requires extensive expertise in measuring the pattern of misalignment in different gaze positions using prisms to optically neutralize the misalignment. The process is time consuming and not widely available in most clinical practices. As a solution, we sought to validate a rapid, automated measurement of strabismus using a head mounted virtual display with video eye tracking.

**Purpose:** We sought to establish the feasibility and accuracy of an automated, objective approach for assessing the horizontal and vertical alignment of the two eyes of normal subjects viewing targets binocularly as a function of gaze position. This was a first step in understanding how well a video-based eye tracking system can assess binocularity. Our purpose was to identify and control factors affecting the accuracy of measuring eye alignment using eye tracking, and to provide normative data upon which to compare patients suffering from double vision.

**Methods:** 20 subjects with normal stereoacuity and without double vision were identified from the University of Iowa campus and gave informed consent. Participants were tested with a head-mounted virtual reality display containing infrared video cameras that recorded the right and left eye position at 100 Hz in conjunction with the development of custom testing and analysis software for this project (Neurolign LLC, Pittsburg, PA). The software presented visual targets for each eye to follow which moved from the center gaze position out to 8 evenly spaced clock hour positions at 10 degrees from center (smooth, linear pursuit test). A second test assessed ocular alignment while the subject's eyes followed an outward spiraling target (smooth, spiral pursuit test). Horizontal and vertical components of ocular misalignment were determined as a function of target location. Here we focused on how well these test paradigms revealed the expected ocular alignment of the two eyes under conditions of binocular viewing of targets.

**Results:**
The mean and standard deviation of the horizontal and vertical components of ocular alignment for each of the 9 cardinal gaze positions are summarized below. Misalignment is expressed in units of prism diopters; 1 prism diopter equals 0.5 degrees of visual angle misalignment. This software provided horizontal and vertical alignment of both eyes in each of the 9 cardinal gaze positions within the measurement accuracy of expert clinical assessment using prisms, which is 1-2 prism diopters. The mean and standard deviation of each of these values were calculated and are displayed in figures included in our presentation.

**Conclusion/Discussion:**
The current testing paradigm revealed horizontal and vertical alignment of the two eyes in the 9 cardinal gaze positions within the measurement accuracy of expert clinical assessment using prisms (e.g 1-2 prism diopters). This approach shows promise for precise, rapid quantification of strabismus. Our next step is to test patients with strabismus in which the pattern of misalignment as a function of gaze position has been clinically characterized. The automated software's portability can potentially provide rapid and remote testing when prompt triage is necessary.

**Title:** Developing an in vivo model for Rabl6a overexpression
**Name:** Samual Hatfield
**Principle Investigator:** Dawn Quelle, PhD
**Collaborators:** Ellen Voigt, Josh Lingo, Courtney Kaemmer, Rebecca Dodd, PhD, Benjamin Darbo, MD, PhD

**Background:** Malignant peripheral nerve sheath tumors (MPNSTs) are the leading cause of death in patients with neurofibromatosis type 1 (NF1). Patients with NF1 develop benign lesions over their lifetime called benign plexiform neurofibromas (PNFs) that can transform into MPNSTs. However, only 30% of PNFs undergo this transformation to malignancy due to unclear mechanisms. We identified a potential driver in these lesions called RABL6A, an oncogenic RAB-like GTPase and found that it is elevated in human MPNSTs relative to PNFs. We hypothesize that RABL6A overexpression drives benign PNF transformation into MPNSTs To further explore the role of RABL6A in PNF to MPNST progression, we have acquired a novel Cre-inducible HA tagged Rabl6a overexpressing mouse model.

**Specific Aims:** The goal of this study is to characterize this mouse model by verifying Rabl6a overexpression within derived Mouse Embryo Fibroblasts (MEFs).

**Methods:** MEFs were generated from mice pregnant with transgenic embryos. PCR was used to confirm presence of the Cre-inducible transgene in the MEFs. Cells were infected with AdCreGFP virus and validated with immunofluorescence to determine presence and cellular localization of the expressed Rabl6a and HA tag.

**Results:** The PCR results determined the presence of the transgene in the majority of MEF lines with 6 positive and 1 negative lines. Immunostaining for the HA tag demonstrated weak cytosolic expression of the transgene when compared to genotypically negative controls following Cre induction. Staining for Rabl6a showed weak staining in controls and strong signal in the cytosol of the MEFs with transgene.

**Conclusions/Discussion:** Our studies support the successful generation of our Cre inducible HA tagged Rabl6a overexpressing transgenic mouse model. However, more comprehensive analysis of the transgene expression and function is needed. While there was observed weak HA expression and modest Rabl6a overexpression in the transgenic MEFs infected with AdCre, the staining only provides preliminary evidence of the transgene's functionality. As this is a novel murine line with unknown characteristics, further optimization of MEF staining protocols is necessary to confirm functionality of the Cre-LoxP system in this line. In addition, these data demonstrate only modest expression of Rabl6a despite overexpression which may be due to high concentrations of the protein causing cellular toxicity. Rabl6a is an oncogene, and elevated expression in cells can lead to cell cycle arrest and death which may affect the transgene function in this mouse model.

**How Providers Screen and Communicate with Patients about Food Insecurity in the Primary Care Setting.**

**Authors**: Marcy Rosenbaum, Kelly Skelly, Stephanie Bunt, Sally Heaberlin

**Background:**
Food insecurity is "a household-level economic and social condition of limited or uncertain access to adequate food" and has been identified as a hidden epidemic which has expanded with the recent COVID pandemic. Increased attention has been given to the importance of health care provider (HCP) assessment of a patient's food security. Little is known about if and how HCPs make the decision to discuss food insecurity with patients. Stereotypes of what types of patients experience food insecurity may result in patients at risk not being identified. Because HCPS may perceive this as a difficult topic to address in healthcare encounters, opportunity exists to understand how and when they choose to inquire about food insecurity. This study seeks to identify how HCPs make the decision to screen patients for food insecurity and barriers and bias that may impact screening.

**Methods:**
As a pilot study, 50 urban and rural HCPs will be surveyed about their decision-making process when screening patients for food insecurity. A subset of respondents will participate in in-depth interviews exploring food security screening experiences and attitudes. Initial survey and interview data will be used to develop more salient survey questions to be distributed to all primary care physicians (N-310) who participate as volunteer subjects in an established statewide research network.

**Findings:**
Findings from the project should help identify how many providers regularly ask patients about food security and how and when they choose to do this. In addition, barriers and effective approaches to these conversations will be identified.

**Discussion:**
Understanding food security screening practices and barriers can support identification of patients facing this health challenge and HCPs communication needs in engaging in food security conversations.

**Feedback request:**
Interpretation of initial data and construction of final survey

# Single Cell Analysis and TCR Sequencing of Immune Cells and Keratinocytes in a Murine Model of Alopecia Areata

Nicholas Henderson, Ali Jabbari, Sam Connell, Payton Kahl, Maddi Lensing

## Background Information

The hair follicle (HF) is a site of immune privilege (IP), and the collapse of this IP is thought to a critical step in the pathogenesis of Alopecia Areata (AA). IP protects HF components from immune mediated attacks by a variety of mechanisms, including physical barriers that reduce lymphatic permeability, downregulation of major histocompatibility complex (MHC) class I expression, and local expression of immunoregulatory molecules [1]. IP environment also normally suppresses natural killer (NK) cells activation by downregulating MHC class I chain-related gene A (MICA) and UL16 binding protein (ULBP) in immune cells that reside in the skin. These would otherwise bind to NKG2D-activating receptors on NK cells and CD8+ T cells which would induce inflammation and damage local tissue [2]. Cytotoxic CD8+NKG2D+ T cells and interferon-$\gamma$ (IFN- $\gamma$) have been demonstrated to play important roles in the development of AA. CD8+NKG2D+ T cells infiltrate the hair follicle of AA and initiate a cascade of events that includes production of IFN- $\gamma$. This potent immune signal impacts HF IP maintenance by inducing expression of MHC molecules and NKG2D ligands in the HF which will, in turn, promote the activation and survival of CD8+NKG2D+ T cells [3] in a self-perpetuating positive feedback loop.

## Purpose of Study

Alopecia Areata (AA) is an autoimmune disease of the hair follicle that affects 1.7% of the general population, and its prevalence ranges from 0.1-0.2% worldwide [4]. AA disease manifestations can vary from well-defined alopecic patches, total scalp hair loss (alopecia totalis, AT), to complete body hair loss (alopecia universalis, AU) [5]. AA impacts quality of life and has substantial psychological outcomes for both men and women [6]. Recently, the FDA approved the first systemic drug, baricitinib, for AA; however, this medication carries the potential for worrisome side effects including increased risk of cancer, thromboses, and myocardial infarctions as well as an increased rate of all-cause mortality. AA treatments therefore still represent a great medical need. Despite recent strides in our comprehension of AA disease mechanisms, the specific interactions between immune effectors and the HF epithelium have not been well-defined. A deeper understanding of how the skin-infiltrating immune cell population interacts with the HF epithelium is critical to identifying pivotal pathogenic pathways and delineating novel treatment targets.

## Methods

We used single-cell RNA-sequencing and T cell receptor (TCR)-sequencing in order to identify cellular and transcriptomic signatures associated with disease. Briefly, CD45+ immune cells from skin and lymph nodes were flow sorted from unaffected (UA) C3H/HeJ mice and C3H/HeJ mice that exhibited AA. Follicular epithelial cells were identified as EpCAM+ Sca-1- cells and flow sorted from dissociated skin from the aforementioned UA and AA mice as well as young unaffected C3H/HeJ mice whose pelage was in synchronized anagen phase. Library prep was performed for 5′ gene expression and TCR sequencing using Chromium (10x Genomics) and Illumina sequencing technologies. Libraries were pooled based on tissue type and mouse group and run on separate lanes on an Illumina HiSeq 4000[7].

## Results

Two methods of digestion were utilized to determine what yielded the highest cell count for flow sorting. Mechanical breakdown of the skin using scissors and enzymatic digestion of the skin incubated with collagenase 1 at 37 degrees Celsius for 1 hour yielded, on average, around 1500 T cells per half gram of UA skin. Another technique that consisted of mechanical digestion using scissors and enzymatic digestion of the skin incubated with Liberase TL for 1 hour and 50 minutes at 37 degrees Celsius followed by a 10 minute incubation of trypsin at 37 degrees Celsius yielded, on average, around 6000 T cells per half gram of UA skin. The differences between the two methods of digestion were also evident when isolating EpCAM+ Sca-1- cells. The skin samples that received the collagenase 1 treatment had a much lower cell yield of EpCAM+ Sca-1- as compared to the skin samples that received the Liberase TL and trypsin treatment.

## Discussion

Optimization of the skin cell isolation protocol has increased the availability of cells for flow selection by magnitudes. This increase in cell yield will allow for more diversity in the downstream analysis of the single-cell RNA-sequencing and TCR-sequencing of the EpCAM+ and CD45+. With this tool, insight into the relationship of the HF epithelium and immune cell landscape can provide a deeper understanding of AA pathogenesis.

**Improving transgender health care by inclusion of evidence-based information on laboratory testing in the electronic medical record**

Nicole Hines
Faculty mentor/supervisor: Matthew Krasowski, MD, PhD (Dept. of Pathology)
Collaborators: Katherine Imborek (Dept. of Family Medicine), Dina Greene (University of Washington-Seattle)

**Background:** Transgender people experience incongruence between gender identity (an individual's personal sense of gender) and sex assigned at birth (SAAB). 'Gender-expansive' is a broad umbrella term that includes transgender, non-binary, and other gender identities. In the last several years, the University of Iowa Hospitals and Clinics (UIHC) has incorporated fields for sexual orientation and gender identity (SOGI) into the electronic medical record (Epic). Patients can volunteer this information at registration, during clinic appointments or hospital visits, and using the patient portal Epic MyChart. Possible information in the SOGI fields include SAAB, gender identity (including options such as transgender male, transgender female, non-binary, and other), and legal sex. "Choose not to disclose", "Uncertain", or "Unknown" are also options for some SOGI fields.

**Aims:**

1. To ascertain voluntary participation in sex/gender identity fields in the electronic medical record (Epic), especially in individuals who identify as transgender and non-binary

2. To identify what combinations of responses are most common in those who are gender-expansive and in those who are taking gender-affirming therapy such as hormones

**Methods:** In this IRB approved project, retrospective data sets were generated using Epic Reporting Workbench, with two main searches that included chart review for selected categories. The first search assessed how often patients provided SOGI information, along with the common patterns of how gender-expansive patients identify in the voluntary SOGI fields. The second search focused on previous orders of laboratory tests that are known to change with hormonal therapy.

**Results:**

For patients 12 years and older seen at UIHC since 2018, 25.7% have voluntarily supplied gender identity or SAAB or both. Gender-expansive patients (as verified by chart review) were found to identify by 3 main patterns of SOGI responses. The first and most common pattern consists of patients that select Transgender or Non-binary for gender identity. The second pattern includes patients who do not select Transgender or Non-binary but have incongruence between gender identity, legal sex, and SAAB (e.g., female for SAAB but male for gender identity). Some combinations imply official change of legal sex. The third pattern consists of those that select "Other" or "Choose not to disclose" for gender identity and/or SAAB. Those taking gender-affirming hormone therapy most commonly identified as transgender male or transgender female or a combination of responses that implied change of legal sex (90% or higher on hormones). Of those selecting non-binary for gender identity, 20.2% were on hormone therapy.

**Conclusion/Discussion:**

Gender-expansive patients identify in SOGI fields in a variety of ways, some are which are straightforward to interpret. SOGI field options such as "Other" and "Choose not to disclose" add complexity but may be selected for reasons such as avoidance of discrimination or for specific gender-expansive identities (e.g., gender queer, fluid, agender) not included in the dropdown options available in Epic. Those identifying as transgender in the SOGI fields were found to have higher rates of gender-affirming hormone therapy than their non-binary counterparts. Patients with incongruence between legal sex and SAAB also had high rates of hormone therapy. This is expected as one requirement for changing the legal sex marker is a permanent physical change (such as hormone therapy or gender-affirming surgery). Furthermore, patients that selected "Other" or "Choose not to disclose" included those who are gender-expansive but with low rates of gender-affirming hormone therapy. Future directions include analyzing the impact of gender-affirming therapy on laboratory testing with the goal of incorporating this information into the electronic medical record.

**Predictors of Osteoarthritis in U.S. Adults: An Epidemiological Study of the National Health and Nutrition Survey (2005 – 2018)**

Ayobami Ogunsola, MD, MPH[1], Arman Hlas, BS[2], Michael Marinier, BS[2], Jacob Elkins, MD, PhD[1,2]

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[2]*University of Iowa Roy J. and Lucille A. Carver College of Medicine*

**Background:** Osteoarthritis (OA) is the most common joint disorder and leading cause of disability in the U.S. population. Current estimates project OA accounts for $16.5 billion dollars in total healthcare spending annually, leading to increased financial burden on both patients and the healthcare system broadly. Historically, OA has been thought to arise from excessive joint loading and degeneration of articular surfaces over time. However, recent studies suggest the mechanism of OA may be more complex, with strong risk factors including age, sex, obesity, and previous joint injury. Obesity, quantified through body mass index (BMI), has been theorized to impact OA by increasing joint load and inflammatory cytokine signaling, limiting mobility, and exacerbating other related health conditions that impact OA. Other patient factors such as race/ethnicity, cigarette use, physical activity level, comorbid medical conditions such as hypertension and diabetes, and indicators of socioeconomic status (SES) such as education and income levels have also been associated with OA progression. While obesity remains a well-characterized risk factor for OA development, less is currently known about other patient factors and how they relate to OA in context of their obesity status.

**Purpose:** The goal of this study was to identify the association between OA and other health predictors among U.S. adults. An additional aim of this project includes sub-analysis of the relationship between OA and other health contributors across varying levels of BMI.

**Methods:** National Health and Nutrition Survey (NHANES) data of adult participants (>18 years) from 2005 to 2018 was reviewed. OA was assessed based on physician diagnosis, and other variables were assessed based on patient-reported data, laboratory data, and examination data. A multivariable survey logistic regression model was used to estimate adjusted odds ratios (aOR) and confidence intervals (95% CIs).

**Results:** A total of 42,143 participants were included in this study. OA was most prevalent at ages ≥ 65 years (n = 2111; 45.23%) and females (n = 2571; 64.49%). The risk of OA increases generally with aging and is more among the female population (aOR = 1.33, 95% CI: 1.25 - 1.42). There is a direct relationship between depression and osteoarthritis (Mild/moderate aOR = 1.66, 95% CI: 1.53 - 1.80; Severe aOR = 2.54; 95% CI: 2.24 - 2.89). The diagnosis of hypertension (aOR = 1.48; 95% CI: 1.38 - 1.60) and diabetes mellitus (aOR = 1.27; 95% CI: 1.15 - 1.39) both increase the risk of developing OA.

**Conclusion:** Depression, hypertension, and diabetes are directly associated with osteoarthritis. Further studies are necessary to elucidate the mechanisms of these associations. This study's findings will encourage the need for a multidisciplinary and holistic approach to the care of osteoarthritic patients.

**Predicting executive function following early-onset acquired brain lesions**

Paige Howard
Mentor: Aaron D. Boes
Other Collaborators: Alyssa W. Sullivan, Jax D. Skye

**Background/Intro:**

Pediatric brain injuries are extremely impactful to childhood development. Many questions remain regarding the relationship between the location of the brain injury (i.e., lesion location) and specific deficits when brain injury occurs in childhood. If we can better understand cognitive outcomes following a pediatric stroke or brain injury, clinicians could utilize a more personalized prognosis by using the lesion location to predict expected deficits. Currently, lesion-symptom mapping has been used in adult stroke and brain injury populations to identify lesion locations that are associated with lower scores in different cognitive domains. These maps can also be used to predict outcomes after stroke or brain injury based on the lesion location in independent cohorts of patients. It remains unknown whether these lesion-symptom maps including adult-onset data can be useful for predicting outcomes when the onset of brain injury occurs in childhood.

**Purpose of study/hypothesis:**

To evaluate whether a lesion-symptom map of executive function (i.e., the Trailmaking Test) derived from subjects with adult-onset lesions can be utilized to make predictions about executive function abilities of subjects with developmental-onset (< 18 years) lesions, based on their lesion location.

**Methods:**

Participants were selected from the University of Iowa Neurological Patient Registry. Inclusion criteria were: focal brain damage and completion of both parts A and B of the Trail Making Test, at least three months after injury. The Trail Making Test is a test of executive function. Lesion-symptom maps were derived using data from individuals with adult-onset (onset > 18 years) lesions. Lesion-symptom maps produced a matrix of voxel values (N) weighted by their multivariate association with the associated cognitive measure and an eigenvalue (l). The lesion masks from the developmental-onset (onset < 18 years) participants were entered into R as a matrix (M). Lesion-symptom map predictions (LSM-P) were derived, as performed in LESYMAP's lesymap.predict function, by multiplying M, N, and l. Predictions were generated for Trails B-A scores. Predictive strength was evaluated using Pearson's correlations (r) and permutation testing for statistical significance.

**Results:**

The adult-onset lesion-symptom maps significantly predicted outcomes of the developmental-onset sample ($r = 0.54$, $p < 0.001$).

**Conclusion/discussion:**

A lesion-symptom map derived from individuals with adult-onset brain lesions significantly predicted executive function outcomes for patients with developmental-onset focal brain lesions. This research could be used in future clinician encounters to better predict patient prognosis and expected deficits after a brain injury, based on the lesion location. Further studies could continue predictions with other cognitive domains, as there are likely differences in effectiveness of this prediction model based on the cognitive domain in question.

**Neuropeptide S (NPS) neurons: parabrachial identity and novel distributions**

Dake Huang, Richie Zhang, Silvia Gasparini,
Miriam C. McDonough, William J. Paradee, and Joel C. Geerling

Neuropeptide S (NPS) increases wakefulness. A small number of neurons in the brainstem express *Nps*. These neurons are located in or near the parabrachial nucleus (PB), but we know little about their ontogeny, connectivity, and function. To identify *Nps*-expressing neurons within the molecular framework of the PB region, we used *in situ* hybridization, immunofluorescence, and Cre-reporter labeling in mice. The primary concentration of *Nps*-expressing neurons borders the lateral lemniscus at far-rostral levels of the lateral PB. Caudal to this central cluster, *Nps*-expressing neurons scatter through the PB and form a secondary concentration medial to the locus coeruleus (LC). Most *Nps*-expressing neurons in the PB region are *Atoh1*-derived, *Foxp2*-expressing, and mutually exclusive with neurons expressing *Calca* or *Lmx1b*. Among *Foxp2*-expressing PB neurons, those expressing *Nps* are distinct from intermingled subsets expressing *Cck* or *Pdyn*. Examining *Nps* Cre-reporter expression throughout the brain identified novel populations of neurons in the nucleus incertus, anterior hypothalamus, and lateral habenula. This information will help focus experimental questions about the connectivity and function of NPS neurons.

**Title: Rural Adolescent Attitudes and Use of Equestrian Helmets**

**Authors: Brianna Iverson, Devin Spolsdoff, Pam Hoogerwerf, Kristel Wetjen, Charles Jennissen**

**Background:** Equestrian helmets can prevent the number and severity of serious head injuries when on or around a horse. Our study objective was to evaluate the frequency of equestrian helmet use in rural adolescents and their attitudes with regards to helmets.

**Methods:** An anonymous survey was conducted of a convenience sample of 2022 Iowa FFA (formerly Future Farmers of America) Leadership Conference attendees. Descriptive, bivariate, and multivariable logistic regression analyses were performed.

**Results:** 1,331 adolescents between 13-18 years of age participated; 41% were males and 95% were Caucasian. Just over half lived on a farm, one-fifth resided in the country but not on a farm, and 28% lived in town. Just over a quarter (26%) of households owned a horse. Slightly less than half (45%) reported they had ridden a horse in the past year. Of these, 57% had ridden a few times a year or less, 12% rode monthly, 16% rode weekly, and 15% rode daily. Females had higher percentages riding more frequently than males ($p<0.001$). Equestrian helmet use was: 13% always, 10% mostly, 11% sometimes, 17% rarely and 50% never. Females had higher proportions always or almost always wearing a helmet (27%) as compared to males (14%, $p<0.01$). Helmet importance (rated 1-10) had a median of 6 and a mean of 5.8; a mean lower than dirt bikes (8.30) and motorcycles (8.6). Younger adolescents (13-16 years), females, and those that resided in the country, but not on the farm rated the importance of helmet use higher than their peers. Those who had not ridden or infrequently rode a horse viewed equestrian helmet use as being more important than more frequent riders ($p<0.001$). Over one-fifth (22%) believed there should be a law mandating equestrian helmet use. Males, Caucasians, and those who lived on farms had lower proportions supporting laws requiring helmet use. Respondents who had participated in an activity that required equestrian helmet use had higher percentages that reported wearing helmets, viewed wearing helmets as important, and supported laws mandating helmet use (all $p < 0.001$).

**Conclusion**: One-half of study adolescents never use equestrian helmets when riding. However, those who had participated in an activity mandating helmets had higher helmet use and ratings of helmet importance. Requiring helmet use at training centers, competitions, club events and group rides may help increase general equestrian helmet use and decrease head injuries.

# Changes in IgG levels in patients treated with plasma exchange using 5% albumin with or without IVIG vs plasma

Claire Jager, Kai Rogers, Gail Nelson, and C. Michael Knudson

**Introduction**: Plasma exchange (PLEX) is commonly used to treat a wide variety of disorders that are thought to be antibody mediated, including antibody-mediated rejection (AMR) of transplanted solid organs. Following a plasma exchange, re-equilibration and synthesis of IgG occurs over 48-72 hours, which is thought to result in a rebound effect of normal and pathological antibodies. Common replacement fluids used during plasma exchange are 5% albumin and plasma. At UIHC, renal AMR patients are given 5% albumin as a primary replacement fluid as well as low dose IVIG after each procedure. Lung AMR patients are given plasma as a primary replacement fluid. The efficacy of these two treatment protocols in their ability to maintain serum IgG levels and therefore prevent the rebound of pathological antibodies has never been compared.

**Hypothesis & Goals**: The goals of this study are 1) compare treatment protocols in their ability to maintain IgG levels in the setting of AMR and 2) perform a cost comparison of raw materials used in each of these protocols. We hypothesized that using plasma as a primary replacement fluid in PLEX maintains serum IgG levels at least as well as 5% albumin and low dose IVIG and would be cost effective.

**Methods**: Plasma samples were collected from consented subjects prior to each procedure and evaluated for IgG concentration. Three patient groups were compared: 1) patients receiving 5% albumin as a primary replacement fluid and no IVIG, 2) patients receiving 5% albumin as a primary replacement fluid and low dose IVIG after each procedure (renal AMR patients), and 3) patients receiving plasma as a primary replacement fluid and no IVIG (lung AMR patients). Estimated and actual costs of raw materials were calculated for renal and lung AMR patients.

**Results**: Patients given 5% albumin as a primary replacement fluid and no IVIG exhibit a significant decline in serum IgG over a series of PLEX procedures. This decline appears to be mitigated by the administration of IVIG after each PLEX ($p=0.11$). Patients treated with plasma as a primary replacement fluid were able to maintain IgG levels better than patients exchanged with 5% albumin only ($p=0.0007$) but not significantly better than patients treated with 5% albumin and low dose IVIG ($p=0.06$). The cost of materials to treat a renal AMR patient in this study with 5% albumin and low dose IVIG was 2.7 times higher than the cost to treat a lung AMR patient with plasma. Using plasma as a primary replacement fluid increases the total procedure time by approximately 30 minutes for every 3 liters processed.

**Conclusions**: Plasma may be a preferable primary replacement fluid type in the treatment of AMR with PLEX. Patients undergoing PLEX with 5% albumin and no IVIG exhibit a significant decline in serum IgG levels, which is though to contribute to a rebound effect of pathological antibodies. The use of plasma as a primary replacement fluid mitigates this decline in serum IgG at least as well as 5% albumin with low dose IVIG. Furthermore, using plasma instead of 5% albumin and low dose IVIG would result in significant savings in total cost and patient time. More clinical trials are needed to investigate the differences between plasma and 5% albumin in their ability to maintain serum IgG levels and prevent the rebound of pathological antibodies. More studies are also needed to elucidate the mechanisms behind the rebound effect and determine the factors involved in upregulating antibody synthesis.

**Title:**
Understanding HPV Vaccine Promotion in Otolaryngology Clinics

**Authors:**
Emily Janio, Eliza Steere, Helaina Thompson, Cori Walker, Aaron Seaman, Natoshia Askelson, Nitin Pagedar

**Background:**
Human papillomavirus (HPV) is a sexually-transmitted virus that has infected nearly half of the US adult population. The virus is a risk factor for several cancers. In 2006, the FDA approved a vaccine to prevent HPV-related cervical cancer. While the incidence of these cancers has declined, the incidence of HPV-related oropharyngeal cancers has increased. These oropharyngeal cancers now compose the greatest number of HPV-related cancers: more than 15,000 diagnoses per year. In 2020, the FDA approved the HPV vaccine as a method of preventing oropharyngeal cancers. Despite these developments, HPV vaccination in the US remains low: just over half of eligible adolescents have received the vaccine. For this reason, identifying novel methods of increasing vaccination rates is necessary.

**Purpose:**
Vaccine uptake may be effectively promoted in otolaryngology clinics. Otolaryngologists are most often responsible for diagnosing and/or managing oropharyngeal cancers. These providers also treat adolescents who are eligible to receive the HPV vaccine. Despite having these encounters, otolaryngology patient visits have not traditionally been leveraged as avenues of promoting vaccination. Thus, there is a need for interventions aimed at increasing HPV vaccine uptake in these settings. In order to inform these interventions, it is necessary to understand the opportunities for vaccine promotion in these environments. We aimed to fill this gap in knowledge through a qualitative study.

**Methods:**
Interviews were conducted with otolaryngologists practicing in the US at both private and public non-academic clinics. Interviews comprised open-ended questions pertaining to otolaryngologists' practices, barriers to, and facilitators of promoting HPV vaccination uptake. Interview recordings were transcribed and coded. This text then underwent thematic analysis.

**Results:**
Fourteen otolaryngologists were interviewed. Regarding barriers to promoting HPV vaccination, providers reported that it was difficult to discuss the vaccine when it was not directly relevant to the patient's immediate concern. However, they noted that it may be feasible to discuss the vaccine during follow-up visits after the patient's acute needs have been addressed. Alternatively, our analysis revealed educational intervention opportunities: participants reported being willing to distribute reading materials pertaining to the vaccine to their patients. In all cases, participants stressed the importance of the vaccine remaining readily available for their patients.

**Conclusions:**
It may not be feasible for otolaryngologists to promote HPV vaccination in every patient encounter. However, these specialists can distribute educational materials or utilize the continuity of their patient's care to encourage vaccine uptake. Collectively, these findings can be used to inform future interventions aimed at increasing HPV vaccine uptake in otolaryngology clinics.

**THREE-DIMENSIONAL ASSESSMENT OF RESIDUAL DEFORMITY IN ADULT CLUBFOOT PATIENTS TREATED WITH THE PONSETI TECHNIQUE AND ITS RELATIONSHIP WITH PATIENT REPORTED OUTCOMES**

Student: Ryan Jasper, M2 with mentors: Dr. Jose Morcuende and Dr. Cesar de Cesar Netto

**Background:** Clubfoot is one of the most common congenital orthopedic abnormalities affecting nearly one in 1000 births. It is characterized by equinus, cavus, varus and adduction deformities. The gold standard of treatment for this condition is the Ponseti method, which utilizes manipulation and casting (figure 1) to sequentially correct malignment. While studies on this treatment method have proven its effectiveness in children, few studies have looked at the long-term residual deformities for these patients as adults and none have utilized weightbearing computed tomography (WBCT) 3D imaging.

**Purpose:** The purpose of this study was to assess residual deformities in adult clubfoot patients treated using the Ponseti method by comparing semi-automatic 3D WBCT scan measurements to a control group and relating these findings to patient reported outcomes (PROs). Our hypothesis was that clubfoot patients would demonstrate significant residual 3D foot malalignment when compared to a matched-control cohort of volunteers and that increased residual malalignment would negatively impact PROs.

**Methods:** This was a prospective, comparative and controlled, IRB-approved study that included 37 patients (57 feet) treated for congenital clubfoot using the Ponseti method and 14 healthy volunteers (28 feet) that were matched based on age, gender, BMI, and had no prior history of foot and ankle disease or injury. All participants were evaluated in a bipedal standing position using WBCT imaging. Alignment of the foot and ankle was found using Foot and Ankle Offset (FAO), a validated semi-automatic measurement of global 3D foot and ankle deformities. FAO measures the 3D relationship between the weightbearing foot tripod (calcaneus, first metatarsal, and fifth metatarsal) and the center of the ankle joint (figure 2). Additionally, several automatic 2D measurements of cavus (talus-first metatarsal and calcaneal inclination angles), varus (hindfoot moment arm and talocalcaneal angle), and adduction deformities (talonavicular coverage angle) were assessed. Normality of the measurements was established using the Shapiro-Wilk test. Measurements were compared between the clubfoot and control groups using either paired T-tests or paired-Wilcoxon tests depending on the normality of the distribution. Responses to patient reported outcome measurement information system (PROMIS) Global Physical Health, PROMIS Physical Function, PROMIS Pain Interference, Pain Catastrophic Scale (PCS), Visual Analog Scale (VAS) for pain, and the European Foot and Ankle Society (EFAS) scores were gathered using the RedCap software. Responses were then correlated with malalignment measurements for clubfoot patients using a multivariate regression analysis. Bivariate analyses were then performed on the measurements found to be significant. P-values of less than 0.05 were considered significant and 95% confidence intervals were reported.

**Results:** Interestingly, no significant overall residual 3D deformity was observed in clubfoot patients when compared to controls, with similar FAO measurements observed between the groups, clubfoot=2.4% (95% CI=1.3°-3.5°) and control=3.2% (CI=1.6°-4.8°, P=0.42). This finding highlights the efficacy of the Ponseti technique in treating clubfoot deformity and aligning the foot tripod to the center of the ankle joint. However, measurements of residual cavus, varus and adduction deformity were significantly different in clubfoot patients. The sagittal talus-first metatarsal angle was found to be significantly larger in clubfoot patients, -0.1° (CI=-3.0°-2.8°), compared to the control group, -5.2° (P=0.04, CI=-9.4° to -1.1°) as seen in figure 3. Clubfoot patients also had a decreased calcaneal inclination angle relative to the controls, 13.0° (CI=11.5°-14.6°) and 21.5° (CI=19.4°-23.8°) respectively (P<0.001). Talocalcaneal angle for clubfoot patients in both the sagittal plane, 44.3° (CI=41.7°-46.9°), and axial plane, 17.7° (CI=15.0°-20.5°), were significantly reduced compared to the control group, 57.5° and 25.8° (CI=53.8°-61.2°, P<0.001 and CI=21.9°-29.7°,P=0.012) respectively. The talonavicular coverage angle in the clubfoot group was 18.6° (CI=15.3°-21.9°), which was significantly less than the control group, which was 29.2° (CI=25.2°-33.2°, P<0.001). The hindfoot moment arm was also found to be significantly reduced in the clubfoot group, 3.8mm (CI=1.9mm-5.6mm), compared to the controls, 7.6mm (CI=5.0mm-10.3mm, P=0.02). The averages of the PROs were 3.4 (CI=2.2-4.6) for VAS, 47.4 (CI=43.9-50.8) for the PROMIS Global Physical Health, 14.6 (CI=11.5-16.8) for EFAS, 8.8 (CI=5.2-12.4) for PCS, 49.9 (CI=45.9-54.0) for PROMIS Pain Interference, and 50.2 (CI=46.3-54.1) for PROMIS Physical Function. VAS scores from clubfoot patients were found to be significantly correlated with the talus-first metatarsal angle in the sagittal plane (P=0.032), with overcorrection of the first ray deformity being associated with increased pain. The talocalcaneal angle in the sagittal plane was found to be significantly correlated with EFAS score (P=0.001) and PROMIS Physical Function score (P=0.002), with lower angulations negatively impacting outcomes.

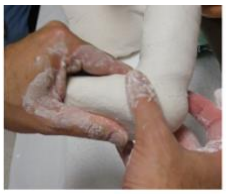

Figure 1.

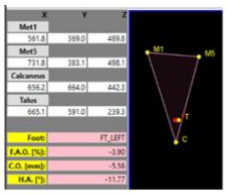

Figure 2.

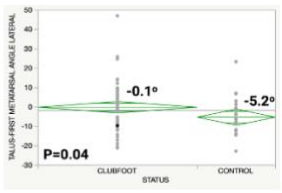


Figure 3.

**Conclusions/Discussion:** In this prospective comparative study with adult clubfoot patients treated with the Ponseti technique during childhood and healthy controls, we observed no significant overall 3D malalignment in clubfoot patients, highlighting the success and efficacy of the Ponseti technique in aligning the foot tripod and the ankle joint. However, when analyzing specific measurements of residual cavus, varus, and adductus deformity, we found that overcorrection of the cavus and under correction of the varus deformity negatively impacted PROs. Our hopes are that the results of our study can guide practitioners when utilizing the Ponseti technique to treat clubfeet patients.

**Title:** The association of pelvic floor disorders with risk factors among parous Ugandan women

JaNiese Jensen
Mentor: Dr. Kimberly Kenne and Dr. Brooks Jackson
Collaborators: Dr. Michael Derrick Ngobi, Dr. Flavia Matovu Kiweewa, Ramya Vemulapalli, Julia Fleecs, and Linder Wendt

**Background**

Pelvic floor disorders (PFD) are a group of disorders involving dysfunction of the pelvic floor resulting in symptoms of anal incontinence (AI), urinary incontinence (UI), and pelvic organ prolapse (POP). It is estimated that 25-50% of women in the United States are affected by PFD. Recognized risk factors for the development of PFD are age, obesity, parity, and mode of delivery. Women with PFD have been found to have a lower quality of life, reduced sexual function, and social abandonment. PFD are not well characterized in low- and middle-income countries (LMIC) even with the known negative impact on a woman's quality of life. The presence of PFD is generally determined by symptom assessment, standardized questionnaires, and a standardized physical exam

**Purpose of Study**

The purpose of this study is to examine risk factors for pelvic floor disorders in parous Ugandan women.

**Methods**

A prospective cohort study was conducted at Makerere University – Johns Hopkins University Research Collaboration (MU-JHU) in Kampala, Uganda. Participants completed a symptom assessment and translated version of standardized questionnaires (Pelvic Floor Distress Inventory- PFDI-20 and Pelvic Floor Impact Questionnaire-7). A standardized physical exam including the Pelvic Organ Prolapse Quantification- POP-Q and Cough Stress Test- CST was completed. Socio-demographic data were obtained from patient interviews and patient medical records. Variables were reported using medians and inter-quartile ranges (IQR) for continuous variables and using counts and percentages for categorical variables. Associations of risk factors with PFD prevalence were evaluated via univariate logistic regression, and reporting using odds ratios and 95% confidence intervals. Institutional Review Board approval was obtained through University of Iowa and MU-JHU.

**Results**

111 women of a planned 150 women were enrolled as of August 22, 2022, with a median age of 35 (IQR 32 – 38), median parity of 4 (IQR 3 – 5), and median BMI of 29 (IQR 24 – 33). All participants are HIV positive and on antiretroviral therapy. The prevalence of any pelvic floor disorders as determined by symptom assessment was 31%. The most common pelvic floor disorder was UI, no participants reported symptoms of AI or POP**.** The most common stage of prolapse as determined by POP-Q was stage II (53%). 55 women (50%) had a positive CST with a median bladder volume of 145 mL (IQR 81 – 235 mL). As defined by symptom assessment there were no significant associations between the presence of PFD and risk factors; age (OR 1.01, 95% CI 0.92 – 1.12), BMI (OR 0.96, 95% CI 0.90 – 1.03), parity (OR 1.01, 95% CI 0.78 – 1.29), or weight of largest infant (OR 1.12, 95% CI 0.57 – 2.16). When compared to only vaginal deliveries, no change in risk of PFD was found for women with only cesarean deliveries (OR 0.31, 95% CI 0.05 – 1.23) or both vaginal and cesarean deliveries (OR 1.31, 95% CI 0.52 – 3.24). As defined by POP-Q stage II or greater cesarean delivery when compared with only vaginal delivery appears to have a protective effect (OR 0.30, 95% 0.08-0.91, p=0.041).

**Conclusion**

Pelvic floor disorders including pelvic organ prolapse and urinary incontinence are prevalent among parous women in Uganda. Aside from a possible protective effect of cesarean delivery, we were unable to identify risk factors associated with pelvic floor disorders in parous Ugandan women.

**Evaluating Severity of Carotid Artery Stenosis Using Cerebral and Ocular Perfusion Metrics**

Matthew Jones, M2
Mentor: Dr. Edgar Samaniego, M.D., M.S., Department of Neurology
Collaborators: Dr. Sebastian Sanchez, M.D.; Rishi Patel, M2

**Background:** Current approaches assessing severity of carotid artery stenosis are based on vessel diameter measurements. These approaches do not capture the true ischemic impact of carotid stenosis because they do not quantify perfusion. Perfusion through cerebral anastomotic networks can serve as collateral flow to compensate for reduced flow caused by carotid stenosis. Perfusion metrics derived from laser speckle flowgraphy (LSFG) allow for analysis of ocular blood flow. *syngo* iFlow (iFlow) extracts cerebral perfusion metrics from digital subtraction angiography (DSA) images by analyzing change in contrast intensity over time. Both tools can be used to investigate perfusion in the setting of carotid stenosis.

**Purpose:** The purpose of this pilot study was to investigate viability of perfusion metrics obtained from LSFG and iFlow as surrogates for the degree of stenosis defined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) protocol.

**Methods:** LSFG and iFlow perfusion metrics were obtained for 14 patients undergoing internal carotid artery (ICA) stenting. LSFG quantified mean blur rate (MBR), an index of ocular blood velocity, in different regions of the eye ipsilateral to ICA stenosis. MBR waveforms were generated by analyzing MBR over time. These waveforms provided additional LSFG metrics for assessing ocular blood flow. iFlow metrics were extracted from seven cerebral regions of interest. Time to peak (TTP), the time at which contrast intensity reached a maximum, was extracted from each location by two raters. TTPs were normalized to account for variability in contrast injection rate and averaged between the raters. Presence of collateral flow was adjudicated by an experienced investigator.

**Results:** Flow acceleration index (FAI) and rising rate (RR), two LSFG metrics quantifying ocular blood flow acceleration, were significantly negatively correlated with NASCET degree of stenosis. FAI and RR also displayed a significant increase after stenting (relative to before stenting). iFlow TTPs were not significantly correlated with NASCET degree of stenosis. Significant TTP decreases were quantified after stenting for all 14 patients. These decreases occurred in three regions distal to stenosis, including the junction of the high cervical and petrous segments of the ICA, the cavernous segment of the ICA, and frontal lobe parenchyma. The decrease in TTP in the frontal lobe parenchyma was not significant for the subset of 11 patients displaying collateral flow.

**Conclusion:** LSFG analysis suggests that FAI and RR are potential surrogates for NASCET degree of stenosis. iFlow shows promise in detecting reperfusion after intervention to treat carotid stenosis. iFlow also may be sensitive to the presence of collateral flow.

**Indications and Amount of Clinical Follow-Up after Mifepristone and Misoprostol for Miscarriage Management, Actual Clinical Use Study**

Mallory Kallish[1], Ravina Vasanwala[1], Dr. Colleen Stockdale, MD, MS[2], and Dr. Abbey Hardy-Fairbanks MD[2]

[1]University of Iowa, Carver College of Medicine

[2]University of Iowa, Department of Obstetrics and Gynecology

**Background:** Early pregnancy loss (EPL) is the most common complication in pregnancy. After diagnosis of EPL, patients have three options: expectant, medical or procedural management. While there have been several studies looking at the outcomes, particularly with respect to the need for repeat procedures, for medical vs. procedural management, no study has attempted to quantify the patient experience or the degree of clinical follow-up after medical or procedural miscarriage management. Therefore, we attempted undertook this study to better understand the clinical course for patients before and after intervention to see how patients respond to treatment and their need for follow-up care in a day-to-day clinical setting.

**Methods:** EPL patients greater than 18 years old were retrospectively identified and classified into a medical (mifepristone and misoprostol) or procedural (uterine aspiration) management group. Exclusion criteria for surgical management included initial procedures done to remove products of conception, emergency uterine aspiration procedures or molar pregnancy. Additionally, patients who initially elected expectant management or patients that were not given multiple management options were excluded from both groups. For both subject groups, information about demographics, successful expulsion of pregnancy, gestational information, the need for any additional medical/procedural management, additional prescriptions, number and type of visits, phone calls, my-chart messages, and ultrasounds were collected.

**Results:** 96 eligible medication patients and 189 eligible surgical patients were identified. The average number of unplanned visits for patients undergoing medical management was .26 vs. .25 for the procedural patients (p=.9052). 6.3% of patients undergoing medical management and 4.23% of the patients who underwent procedural management visited an urgent care or emergency room for issues related to their miscarriage management (P=0.0000005, OR 0.14 (0.06-0.33)). Provider communication via phone call averaged .56 phone calls for medical management patients and .45 phone calls for procedural (p=.35). Medical management patients sent an average of .52 MyChart messages after their procedure, while procedural patients sent an average of .30 (p=.0755). Lastly, the patients in the medical management group averaged 1.24 ultrasounds after diagnosis of miscarriage while surgical patients averaged 1.17 ultrasounds (p=.5073).

**Discussion:** Despite the differences between the two interventions, provider communication (via follow-up visits, phone-calls and MyChart messages) were not significantly different between the procedural and medical intervention groups. There was also no significant difference in the number of follow-up ultrasounds needed. These results suggest that the clinical course after intervention is similar for both medication and procedural management and reaffirms the current standard of practice that allows patients to choose either management. However, the higher percentage of ER/urgent care follow-ups for the medical management group may suggest that problems after medical management are more severe in nature and ultimately more time-consuming and expensive for the patient.

2022 Medical Student Research Conference Poster Abstract

Andreas Kantartzis, M1 (MSTP)

**Title**: The Role of Mast Cells in Malignant Peripheral Nerve Sheath Tumors

**Authors**: Andreas Kantartzis, Amanda Scherer, Jeff Rytlewski, Wade Gutierrez, Qierra Brockman, Gavin McGivney, Alexa Sheehan, Vickie Knepper-Adrian, Rebecca Dodd

**Background**: Malignant Peripheral Nerve Sheath Tumors (MPNSTs) are aggressive sarcomas derived from Schwann cells. Half of all MPNST cases occur in patients with Neurofibromatosis Type 1 (NF1). These patients have germline mutations in one allele of neurofibromin (*NF1*) which leads to RAS hyperactivity and the formation of premalignant lesions called plexiform neurofibromas. Loss of the remaining allele of *NF1* and loss of a tumor suppressor gene results in MPNST formation. We have previously shown that mast cells are enriched in human NF1-associated MPNSTs and that constitutive deletion of mast cells in MPNST mouse models delays tumor initiation. However, the mechanisms by which mast cells contribute to MPNST biology are poorly understood.

**Purpose:** Establish and optimize mast cell degranulation and migration assays to explore functional differences in $Nf1^{+/-}$ mast cells.

**Methods**: Murine bone marrow derived mast cells were differentiated for 5 weeks. WT and $Nf1^{+/-}$ mast cells were activated, and degranulation was induced with stem cell factor (SCF). A fluorescent based beta hexosaminidase assay was conducted to quantify degranulation. To evaluate migration capability, mast cells were incubated for 4 hours in a fibronectin coated transwell, stained with crystal violet, and counted with an inverted microscope. SCF was used as a chemoattractant.

**Results**: We observed increased mast cell degranulation with the addition of SCF. However, levels of SCF-induced degranulation did not differ between WT and $Nf1^{+/-}$ mast cells. We also found that $Nf1^{+/-}$ mast cells exhibit significantly increased migration to SCF compared to WT mast cells.

**Conclusion**: We successfully established and optimized functional assays for quantifying mast cell degranulation and migration. Using these assays, we found that $Nf1^{+/-}$ and WT mast cells show equal levels of degranulation in response to SCF stimulation. We also observed that $Nf1^{+/-}$ mast cells had increased migration toward SCF, a cytokine with heightened expression in $Nf1^{-/-}$ Schwann cells. Future studies will use these assays to test various aspects of a hypothesized mast cell-dependent immunosuppressive loop to gain a better understanding of the role of mast cells in MPNSTs.

**Title:** Association of Cord Blood Cytokine/Chemokine Biomarker Concentrations with Bronchopulmonary Dysplasia (BPD) in Preterm Infants

**Authors:** Rekha Karuparthy, Priya Reddy, Erika Lin, Robert Birkett, Karen Mestan

**Background:** Bronchopulmonary dysplasia (BPD) continues to be the most common chronic lung disease in preterm infants, and specifically affects up to one third of extremely preterm infants (<28 weeks gestation). BPD is defined as having a clinical presentation of chronic oxygen dependence at 36 weeks post menstrual age. The complex mechanisms behind the progression of BPD remains unclear, however, both inflammatory and vascular pathways play a major role in lung injury. Due to the high risk of morbidity and mortality with BPD, it is critical to investigate the potential role that early biomarkers can have in better predicting and managing preterm infants with BPD. This study evaluates inflammatory and vascular cytokine/chemokine cord blood concentrations in relation to BPD, gestational age (GA), and placental domains to provide insight into potential biomarkers for the progression of BPD pathogenesis and its multifactorial pathways.

**Objective:** To examine potential immunological and vascular biomarkers comparing cytokine/chemokine concentrations across GA, placental pathology, and BPD versus no BPD infants to highlight potential predictive models of developing BPD in preterm infants.

**Design/Methods:** Umbilical cord blood samples were collected and stored at Prentice Women's Hospital (Chicago, IL), with parental consent obtained through the Northwestern University Cord Blood and Placental Tissue Biorepository. A sample of 193 births were studied, which included 77 preterm infants who developed BPD, 84 preterm infants who did not develop BPD, and 31 healthy term infants. One infant expired prior to 14 postnatal days and was excluded from analysis, all others were followed to 36 weeks post menstrual age to determine outcomes of BPD as defined by the modified NIH criteria (2018). Potential biomarkers were measured in all 193 cord blood samples using multiplex enzyme-linked immunoassay (ELISA) and were performed in 1:1 dilution using commercially available kits (R&D Systems, Minneapolis, Minnesota). The biomarkers included 20 cytokine/chemokines: Eotaxin, IL1-Ra, IL-6, IL-8, IL-10, MCP-1, MCP-3, M-CSF, MIP-1α, MIP-1β, TNF-α, Angiopoiten-2, G-CSF, Endoglin, Endothelin-1, Leptin, HGF, PLGF, FGF-2, and VEGF-A.

**Statistical Analysis:** Statistical data analysis of cytokine/chemokine concentrations linked to maternal and infant clinical data was analyzed in R-Studio Version 2022.02.3. Wilcoxon Rank Sum test was used to compare differences in median cytokine/chemokine concentration levels. One-way ANOVA was used to determine differences in average raw concentrations across GA groups. Finally, linear and logistic regression models were built to evaluate cytokine/chemokine concentrations in relation to clinical outcomes, specifically BPD.

**Results:** Within the sample of 193 births, GBS status, antenatal IUGR, abruption, GA, birthweight, APGAR scores at 1 and 5 minutes, and placental weight were significantly different between preterm infants who developed BPD compared to preterm infants who did not develop BPD. Birthweight (864 ± 200 g vs. 1120 ± 293 g; BPD vs. No BPD; p=<0.001) and GA (26.2 ± 1.54 weeks vs. 27.2 ± 1.77 weeks; BPD vs. No BPD; p=<0.001) were significantly lower in preterm infants who developed BPD compared to those who did not, which matches numerous past studies. When analyzing the raw median values of cytokine/chemokine concentration values, Eotaxin, MIP-1α, Angiopoiten-2, and Endothelin-1 were significantly increased in preterm infants who developed BPD compared to those who did not. After adjustment for GA, Eotaxin, MIP-1α, Angiopoiten-2, Endothelin-1, and HGF significantly decreased as GA increased, while Leptin significantly increased as GA increased (p=<0.05). Cytokine/chemokine concentration levels were also compared across preterm GA sub-categories based on WHO guidelines: extremely preterm (<28 weeks), very preterm (28-32 weeks), late preterm (32-37 weeks), and term (>37 weeks). Eotaxin, IL1-Ra, IL-6, IL-8, IL-10, MCP-1, MCP-3, M-CSF, TNFα, G-CSF, and Endothelin-1 were significant for differences across the GA spectrum (p=<0.05). In addition, when analyzing GA based on preterm sub-categories with BPD, Eotaxin (OR=1.43 [1.1-1.9]) and Endothelin-1 (OR=1.18 [1.02-1.37]) remained significant (p<0.05). Lastly, placental pathology was analyzed across four domains: acute inflammation (AI), chronic inflammation (CI), maternal vascular malperfusion (MVM), and fetal vascular malperfusion (FVM). With AI, IL-6, MIP-1β, TNFα, G-CSF, HGF, and VEGF-A significantly increased while Leptin was found to significantly decrease AI pathology (p=<0.05). With CI, MCP-3 significantly increased CI pathology while FGF-2 significantly decreased CI pathology (p=<0.05). With MVM, Leptin significantly increased MVM pathology. With FVM, IL-1Ra and MCP-1 significantly increased FVM pathology (p=<0.05). After further adjustment for BPD and cytokine/chemokine concentration levels, no placental pathology remained significant in predicting BPD development.

**Conclusion:** Among the 20 cytokine/chemokines, there are certain biomarkers that are associated with the clinical BPD phenotype, specifically Eotaxin, Angiopoiten-2, MIP-1α, and Endothelin-1. This is the first study to characterize cytokine/chemokines with BPD across the preterm GA spectrum and with placental pathology. Further investigation is warranted to understand the inflammatory and vascular mechanisms that mediate the pathogenesis of BPD.

# Dynamic Ultrasound Measurement of Median Nerve Kinematics in the Carpal Tunnel

Kyle Kato[1], Ignacio Garcia Fleury[2], Jessica Goetz[2,3], Joseph Buckwalter V[2,4]

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**Background:** Carpal Tunnel Syndrome (CTS) is the most common peripheral nerve entrapment neuropathy in the United States. CTS is initially diagnosed by clinical examination and confirmed with electrodiagnostic testing or ultrasound measurements of nerve size. However, patients with early-stage CTS do not always meet the electrodiagnostic or ultrasound criteria for CTS due to the short duration of nerve compression. Dynamic ultrasound provides an alternative to standard practice because it allows for the assessment of median nerve kinematics, including displacement, velocity, acceleration, and strain, which may indicate nerve entrapment in inconclusive CTS cases. The aim of this study is to use ultrasound dynamically to compare median nerve kinematics between CTS patients and healthy individuals during everyday hand movements.

**Methods:** We collaborated with the University of Iowa Hand Clinic to identify patients diagnosed with CTS as well as controls. Patients with diabetes, arthritis, or a history of wrist fractures/surgeries were excluded. Assessed hands were positioned prone, and the ultrasound captured videos of the median nerve during flexion and extension of digits 2-5 individually, gripping, and typing. These videos were analyzed using pattern recognition software to track the median nerve and calculate displacement, velocity, acceleration, and strain.

**Results:** 24 CTS patients and 8 control patients are currently enrolled in this study. We are still actively enrolling patients, focusing primarily on controls that are age and gender-matched to our CTS cohort. Preliminary analysis indicates less displacement in the median nerve of CTS patients compared to healthy individuals, but this will need to be confirmed once our control cohort is complete. Velocity and acceleration evaluation is in progress as well, but those results are not as readily interpreted at this stage. Strain analysis has been challenging due the complexity of the carpal tunnel and video quality obtained by the ultrasound machine. This parameter will be our final focus and may be abandoned if the pattern recognition software is insufficient.

**Conclusions:** Preliminarily, CTS patients appear to have different median nerve kinematics compared to patients with healthy carpal tunnels. We have noted less displacement in CTS, which is expected because that increases the likelihood of nerve compression. We will be able to quantify the differences in displacement, velocity, and acceleration once our control cohort is complete.

**2022 Medical Student Research Conference Abstract**

**Title**: Suprapubic Catheter Use in the Management of Long-Term Bladder Dysfunction: A Single Center Retrospective Chart Review

**Authors**: Faizan Khawaja, Kevin Flynn MD, Bradley Erickson MD

**Background**: Though clean intermittent catheterization (CIC) has been the gold standard for the management of urinary retention (3) some patients may not be candidates for CIC due to difficult anatomy, urinary obstruction, low functional status, or limited upper-extremity function. (5,8) Whilst indwelling urethral catheters are a widely used form of continuous catheterization (5) there remains debate over the safety and long-term outcomes of suprapubic tubes (SPT) in the long-term management of bladder dysfunction. (4-7)

**Purpose/Aims**: This study aims to describe the patients who underwent placement of SPTs at the University of Iowa Hospitals and Clinics, the indications for placement, the rates and severity of short- and long-term complications, and duration of SPT use.

**Methods**: Patient were identified via CPT code 51102 specific to SPT placement procedure and patient MRN, full name, DOB, sex, service date, primary diagnosis, service department, and service provider were captured. A retrospective chart review was then performed to identify whether they met inclusion criteria of SPT placement for long-term bladder dysfunction and capture patient demographics, co-morbidities, indications, surgical approach, 30 day and over 30 day complication types, and patient follow-up. Data was stored in REDCap in a secure fashion.

**Results (Preliminary)**: 191 patients (137 male, 54 female) were identified as undergoing SPT placement for long-term bladdery dysfunction. Median age was 65. Median BMI was 28.2 and 29.6 (male and female, respectively). The indications for SPT placement were acquired neurogenic bladder (n=69), urinary retention (n=52), urethral stricture (n=18), incontinence (n=18), congenital neurogenic bladder (n=13), malignancy (n=8), artificial urinary sphincter explant (n=4), fistula repair (n=4), trauma (n=4), and cystolitholapaxy (n=1). 54 patients experienced a total of 59 incidences of complications within 30 days of SPT placement this included hematuria (n=7), UTI (n=11), catheter displacement n=3), cellulitis (n=11), and other (n=12). 80 patients experienced a total of 130 incidences of complications over 30 days after SPT placement; this included tract stricture (n=2), tube clogging (n=22), recurrent UTI (n=33), recurrent bladder spasms (n=17), other infection (n=7), hematuria (n=14), and other (n=35). At the last known clinic visit, 137 patients still had an SPT in place.

**Conclusion/Discussion**: This study describes the patient population seen at the University of Iowa Hospitals and Clinics who were assessed as suitable candidates for SPT placement for long-term bladder management. The most common indication for SPT placement was acquired neurogenic bladder. UTI was the most common complication within the first 30 days and recurrent UTIs were the most common >30-day complication. 75% of patients continue to use their SPT at the time of last clinic encounter. This preliminary data provides insight into the patient populations who choose to manage their lower urinary tract symptoms with SPTs. It also shows the complications patients and providers may expect within the short and long term, information that has to this date been poorly studied. More work needs to be done into the severity of complications and quantifiable patient satisfaction scores to understand the role SPTs may play as a viable option for continuous catheterization.

**Psychiatric and Obstetric Disease Share Vascular Mechanisms in the RGS2 Knockout Mouse**

Student: Michaela Kiel  Mentor: Mark Santillan, MD, PhD
Other collaborators: Serena Banu Gumusoglu, PhD, Brandon Schickling, PhD, Kaylee Weaver, Marisol Lauffer, MSc, Hannah Sullivan, Kaylie Coulter, Yuping Zhang, Eric Devor, PhD, Donna Santillan, PhD.

**Background:** Preeclampsia is a multifaceted gestational hypertensive disease that involves many tissues and organ systems. Those who develop preeclampsia have increased risk for mood disorders and anxiety; recursively, depression and anxiety increase risk for preeclampsia. The conserved mechanisms underlying this bidirectional risk are poorly understood. Altered G-protein coupled receptor (GPCR) signaling has been implicated in both conditions. For instance, polymorphisms in the regulator of GPCR signaling 2 (*RGS2)* confers clinical risk for preeclampsia, anxiety, and depression. Furthermore, our lab has previously shown that *RGS2* deletion yields placental and physiologic abnormalities similar to those that occur in preeclampsia. Others have shown altered mood and related behaviors in *RGS2* knockout mice.

**Aims:** To investigate the crosstalk between mechanisms of preeclampsia and neuropsychiatric disease within the *RGS2* knockout mouse by assessing pathways that signal through RGS2 and have pathologic roles in depression and preeclampsia (e.g., serotonin, vasopressin).

**Methods:** We used a constitutive *RGS2* knockout mouse model (*RGS2KO)* on a C57B6 background to reveal shared risk mechanisms for preeclampsia and anxiety/depression. Six mice per genotype per sex underwent behavioral tests including the elevated plus maze (EPM) (anxiety-like behavior), open field test (OPT) (locomotor behavior and impulsivity), Y-maze (working memory), 3-chamber social test (sociability), sucrose preference test (anhedonia), and tail suspension test (depressive-like behavior). Vascular function was assessed by tail cuff plethysmography. Aortas (n=3 per genotype per sex) and plasma were collected, and brains were hemisected and evaluated structurally and molecularly via immunohistochemistry (IHC) and qPCR respectively. IHC targets included IB4 Lectin (vasculature) and NeuN (neuronal nuclei). Cortical and white matter thickness and cell density were calculated (ImageJ). RNA was extracted from specific brain regions including the cortex, midbrain, and hypothalamus/ paraventricular nucleus. Expression profiling was done on various serotonergic, oxidative stress, and vascular function genes. Platelet-free plasma serotonin was assessed via a 5HT ELISA All data collection and coding were blinded. Statistical analyses were done in GraphPad Prism. Behavioral data was analyzed to sex-matched controls due to an apriori hypothesis that behaviors would differ by sex. Structural and molecular analyses were analyzed by sex and genotype matched to respective controls. $P<0.05$ was significant.

**Results**: Behavioral studies showed male KO mice exhibited hyperlocomotion in the OFT ($P = 0.05$), inhibition in the Y-maze ($P = 0.048$), and impaired (nonsignificant) social memory in the social preference test in comparison to male controls. Females RGS2KO exhibited anxiety- ($P = 0.05$) and depressive-like respectively ($P = 0.005$) phenotypes on the EPM and TST in comparison to female controls. Both male and female RGS2KO mice exhibited hyperconsumptive/ hedonic behaviors in the sucrose preference test (males: $P = 0.04$, females: $P = 0.02$). Blood pressure was unchanged by sex or genotype. RGS2KO mice exhibited significant reductions in cortical vascular density ($P_{SEX\ x\ GENOTYPE} = 0.005$ genotype main effect driven by males, post hoc tests: males: $P = 0.05$, females: $P = 0.144$). Cortical thickness, white matter, commissural thickness, and cortical cell density were unchanged. Molecular profiling of the cortex, midbrain, and hypothalamus/paraventricular nucleus via qPCR revealed a significant increase in cortical *HTR2A* ($P_{SEX\ x\ GENOTYPE} = 0.004$, genotype main effect driven by females, post hoc tests: males: $P = 0.426$, females: P=0.006), *MAOA* ($P_{SEX\ x\ GENOTYPE} = 0.04$, genotype main effect driven by females, post hoc tests: males: $P = 0.555$, females: $P = 0.03$), and hypothalamic *SLC6A4* ($P_{SEX\ x\ GENOTYPE} = 0.009$, genotype main effect driven by males, post hoc test: males: $P = 0.02$, females: $P = 0.16$), *HO1* ($P_{SEX\ x\ GENOTYPE} = 0.0168$), *NRF2* ($P_{SEX\ x\ GENOTYPE} = 0.0384$), *SOD1* ($P_{SEX\ x\ GENOTYPE} = 0.0253$), *HIF1a* ($P_{SEX\ x\ GENOTYPE} =0.0336$), and *GPX1* ($P_{SEX\ x\ GENOTYPE} =0.0049$). Platelet-free plasma levels of 5-HT were unchanged by ELISA. Aortas from *RGS2KO* mice and wildtype counterparts revealed significant upregulation of *NOX4* ($P_{SEX\ x\ GENOTYPE} = 0.004$, genotype main effect driven by females, post hoc test: males:, $P = 0.181$, females: $P = 0.002$), *HIF-1A* ($P_{SEX\ x\ GENOTYPE} = 0.007$, genotype main effect driven by females, post hoc test: males: $P = 0.125$, females: $P = 0.04$), and *PDGFRb* ($P_{SEX\ x\ GENOTYPE} = 0.008$, genotype main effect, post hoc tests: males: $P = 0.07$, females: $P = 0.05$). *MMP-9* was significantly downregulated in RGS2KO males ($P = 0.05$).

**Conclusion:** Collectively, these results demonstrate that *RGS2*KO mice exhibit sex-specific alterations in mood and other behaviors, in cerebral vascular density, in serotonergic and redox gene expression across the brain, and in peripheral vascular redox systems. Redox and angiogenic dysregulation may underlie vascular changes and link the shared pathogenesis of anxiety/depression to preeclampsia. This points to valuable future therapeutic targets and avenues for further mechanistic exploration.

# DMEK Scrolls at 2,000 Frames Per Second: The relationship between scroll velocity and tissue characteristics

**Authors:** Matthew Kigin, Christopher S. Sales, MD

**Background:** Recent advancements in DMEK surgery have focused on reducing the procedure's duration by pre-preparing the DMEK allograft at an eye bank, reducing surgically induced trauma to the allograft's endothelial cells, and shrinking the cross-sectional size of DMEK tissue injectors to minimize disruption to the recipient cornea. The LEITR modified Jones Tube is the most recent addition to the commercial market and the narrowest injector available. Conventional wisdom has speculated that a narrower injector should cause more endothelial cell damage than a wider one due to the mismatch in cross-sectional diameter between the DMEK scroll and the injector's internal diameter. The rationale is that if the injector's lumen is narrower in cross-sectional diameter than the DMEK scroll, the corneal tissue traveling through it will make obligatory contact with the lumen walls; such contact harms endothelial cells because they reside on the exterior surface of the DMEK scroll. Last summer, we demonstrated that the LEITR injector is not associated with more endothelial cell damage, but we did not understand why. Therefore, we endeavored to better understand this phenomenon by visualizing DMEK scrolls traveling through variable lumen sizes and velocities under high-speed videography.

**Purpose**: To analyze how DMEK scrolls travel through variable lumen diameters at variable flow velocities with respect to the tissue scroll's cross-sectional diameter and its contact with the lumen wall.

**Method(s):** High-speed videography was used to capture images (≤2,000 frames per second) of DMEK scrolls traveling through two custom-made glass tubes shaped similarly to an hourglass with variable cross-sectional diameters. 4 DMEK scrolls were sampled with donor ages 72 and 73 years, which are ages that correlate with slightly greater than average cross-sectional diameters of resting DMEK tissue scrolls. Flow velocities were controlled with a syringe pump and release valve. The wider tube's internal diameter (ID) (1.68 mm) approximated the narrowest aspect of what is considered the standard tissue injector, while the narrower tube's ID (0.88mm) approximated the narrowest aspect of a LEITR modified Jones Tube, which is the narrowest injector on the market. Scrolls were observed at varying velocities (0.007 m/s – 1.56 m/s) through each lumen. Scroll width was measured using digital calipers and compared to the resting scroll width and the lumen diameter, and the high-speed video was analyzed for scroll folding characteristics. A threshold "optimal tissue velocity" in each lumen size was determined to be the average of five successive tissue velocities above which there was no statistically significant difference in scroll width measurements.

**Results:** 40 videos were recorded in total (n=20 per lumen diameter), with ten ejections executed with each DMEK scroll. As tissue velocity increased, scroll width decreased for each tissue in each lumen size (narrow: rest=1.85 ± 0.02mm, slow=1.39 ± 0.08mm, medium=1.19 ±0.03 mm, fast=1.17 ±0.01 mm [$p<0.0001$]; wide: rest=1.84 ± 0.01mm, slow=0.86 ±0.01 mm, medium=0.81 ±0.03 mm, fast=0.77±0.01 mm [$p<0.0001$]). At higher velocities, the tissue scroll did not contact the lumen wall in either the wide or narrow tubes. The "optimal tissue velocity" speed was significantly higher when passing through narrow lumens than wider lumens (1.19m/s ± .09 vs. 0.14 m/s ± .04 [$p<0.01$]). Qualitatively, turbulent tissue characteristics were observed as the tissue velocity increased above the threshold of "optimal tissue velocity."

**Conclusion:** DMEK scroll width is dynamic and depends on flow velocity. In this series, scroll width significantly decreased as tissue velocity increased regardless of the tissue's resting dimensions or injector lumen internal diameter. It is possible for a scroll to travel through a lumen that is narrower than its resting cross-sectional diameter without touching the lumen walls because the scroll decreases in cross-sectional diameter at higher velocities. This may be one explanation for our previous observations that the LEITR injector is not associated with more endothelial cell loss. Further, we observed an asymptotic relationship between flow velocity and scroll width, suggesting there may be an "optimal tissue velocity" that prevents endothelial cell scraping while maintaining surgical control. While the intra-operative implications of this data are yet to be determined, the tissue behavior at various velocities (i.e., the velocity profiles) for both the narrow and wide lumens suggests that it may be possible to reduce endothelial cell damage caused by tissue loading by being cognizant of loading velocity. There may even be potential to implement a more mechanized loading approach to better control tissue loading velocity.

Victor Kilonzo, Mayu Oya, YoungCho Kim, Nandakumar Narayanan

# Prefrontal D1DR-Expressing Neuronal Ensembles in Cognitive Processing

## Abstract

High-level cognitive processing is perturbed in several neuropsychiatric disorders, including Parkinson's disease (PD). One of these processes that is reliably disrupted is working memory, which requires participants to maintain information over a delay. Working memory involves dopamine and the prefrontal cortex which can be impaired in PD. Dopamine acts via D1-type dopamine receptors, which affect excitatory pyramidal neurons and inhibitory GABAergic interneurons. It is unknown how D1DR-expressing pyramidal neurons or D1DR-expressing interneurons are involved in cognitive processing relevant to PD. We aimed to characterize the functional role these two classes of neurons play in mice, as well as determining their contribution to behavioral tasks that assess working memory. We used calcium imaging to measure the neural activity of D1DR-expressing pyramidal neurons or interneurons in freely behaving mice. In D1-Cre mice, we found that D1DR-expressing neurons in the PFC preferentially fire after rewards. Additionally, principal component analysis revealed increased neuronal firing in D1-Cre+ pyramidal neurons over temporal intervals. Lastly, we show the assessment of D1DR-expressing interneurons in the PFC of a new mouse model that restricts calcium sensor expression to neurons that are positive for both D1DR and vesicular GABAergic transporter, an interneuron marker. We plan to utilize an intersectional genetics approach to specifically and selectively record from D1DR-expressing pyramidal neurons and interneurons with calcium imaging technology and fiber photometry when mice undergo working memory tasks. These data will determine how D1DR-expressing pyramidal and interneurons contribute to behavioral outcomes relevant to cognitive dysfunction in PD.

**Abstract**

**The Effect of Transcatheter Aortic Valve Replacement on Surgical Aortic Valve Replacement**
**By: Dr. Mohammed Bashir and Benjamin Kirk**

**Background**

The introduction of Transcatheter Aortic Valve Replacement (TAVR) in 2010 has been one of the major advances in valve therapy over the last decade. It was approved for all risk categories of patients in 2016. Despite this recent innovation, Surgical Aortic Valve Replacement (SAVR) continues to have a significant role in managing patients with aortic valve disease. The SAVR operation has not changed significantly since its introduction several decades ago. This study aims to interpret the effect which TAVR implementation has had on the surgical techniques of SAVR.

**Methods**

This retrospective study utilized the records of 408 UIHC patients who underwent SAVR between 2010 and 2022. With 2016 as the year TAVR was approved for all patients, the patients were divided into two groups based on their operation date. Cohort A underwent surgery before 2016 (200 patients) and Cohort B underwent SAVR after 2016, group of 208 patients. Both groups were then compared for the prosthetic valve size and incidence of root enlargement. Data concerning the subject's pre-existing conditions and post-operative outcomes were also compared.

**Results**

After completion of the chart review, the average prosthetic valve size used in group A was 22.29 mm. In group B, the average prosthetic valve size was 23.85 mm. 7 patients in group A underwent root enlargement, versus 37 patients in group B. In group A, 5 patients received pacemaker implants, while 13 patients in group B received pacemaker implants. Interestingly, the average units of blood given to group A was 1.79, while the average units given to group B was 0.889. More importantly, the average post-op aortic valve mean gradient and severity of aortic valve insufficiency in group A were calculated to be 14.05mmHg and .503, respectively. In group B, the average post-op aortic valve mean gradient and severity of aortic valve insufficiency were observed to be 10.02 and .288, respectively.

**Conclusion**

The use of larger prosthetic valves and the increase of root enlargements performed suggest that the approval of TAVR to all patients has led to the implementation of more aggressive SAVR techniques to compete with the outcomes of TAVR. This has allowed SAVR to remain a viable option for patients. The decrease in post-op average mean gradient and decrease in the severity of aortic valve insufficiency in group B, offers better hemodynamics and in theory should translate to better long-term outcomes. In the future, further analysis of patient outcomes is needed to assess the long-term impacts of TAVR introduction.

# Early Sinus Disease in Newborn Pigs with Primary Ciliary Dyskinesia

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David A. Stoltz, Mahmoud H. Abou Alaiwa

## Introduction

Primary Ciliary Dyskinesia (PCD) is a rare, genetic disorder in which disrupted motile cilia function causes abnormal mucociliary clearance. The paranasal sinuses are hollow spaces of air in the skull and bones around the nose. While their true function remains debatable, they may have an adjunct role to the nasal cavity by producing nitric oxide and aiding immune defenses. In PCD, the lack of functioning cilia results in mucus accumulation within the sinus cavities. Due to this, over 80% of PCD patients have daily nasal congestion, and nearly all PCD patients demonstrate pansinusitis on CT scans. To better understand the role of dysfunctional cilia in the function of the sinuses, we developed a porcine model of PCD with targeted disruption of the *DNAI1* gene. This specific mutation occurs in ~4-10% of people with PCD. We hypothesized that pigs with PCD will develop sinus disease that is seen early in the newborn age.

## Methods

Generation of PCD pigs was done with CRISPR/Cas 9 at the zygote stage which was then cultured into a blastocyst and transferred into a surrogate sow. CT scans of the pig sinuses were acquired with a dual source high-resolution multi-row detector CT scanner (Siemens SOMATOM Force, 120 kVp, 190 mA, slice thickness 0.6 mm, slice spacing 0.3 mm) and reconstructed with a sharp Br59 kernel. All CT scans were 512 × 512 voxels in the transverse plane. The CT DICOM data sets were imported into ITK-SNAP software for initial image segmentation. The thresholding tool was used to separate the desired CT scan components by color intensity. The segmentations done in ITK-SNAP were then uploaded into 3D Slicer for refinement using the paintbrush and eraser tools.

## Results

Newborn pigs with PCD had evidence of mucosal thickening and mucus accumulation in the paranasal sinuses within 24-48 hours after birth. As they grew older, their sinus disease got worse. In some cases, there was complete opacification of the maxillary and ethmoid sinuses. In some other cases, there was opacification and mucus accumulation within the mastoid air space and the middle ear. Most importantly, none of the pigs studied showed signs of infection.

## Conclusions

Pigs with targeted disruption of the *DNAI1* gene have disrupted ciliary function and early sinus disease. These findings recapitulate the clinic findings of humans with PCD.

**Do endothelial biomarkers of oxidative stress associate with endothelial dysfunction in CKD?**

Dariya Kozlova, Colin Gimblet, Linder Wendt, Katharine Geasland, Tamara Hamzeh, Jackson Ernst, Mingyao Sun, Patrick Ten Eyck, Diana Jalal

Patients with chronic kidney disease (CKD) are at an increased risk of cardiovascular disease (CVD). The increased risk of CVD in CKD is not explained by the increased prevalence of traditional (Framingham) risk factors in CKD. Nontraditional risk factors for CVD, such as endothelial dysfunction and oxidative stress, are present in patients with CKD and believed to contribute to the increased risk of CVD. Brachial artery flow-mediated dilation (BA-FMD), a measure of endothelial dependent dilation (EDD), is lower in patients with CKD. Nitroglycerin (NTG) mediated dilation is a measure of endothelium independent dilation (EID). Endothelial expression of nitro-tyrosine (NT) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase are utilized as biomarkers of oxidative stress and associate with endothelial dysfunction in healthy older adults. We hypothesized that endothelial NT and NADPH oxidase associate with endothelial dysfunction in CKD.

Data from the baseline samples of 160 participants with CKD who had participated in 3 clinical trials were included: Curcumin (n=75), Resveratrol (n=19), and urate-lowering studies (n=66). Immunofluorescence was used to analyze the expression of NT and NADPH oxidase and was reported as the ratio of CY3 average pixel intensity relative to HUVEC controls. Previously collected measurements of BA-FMD and NTG mediated dilation were utilized. Generalized linear models were applied. The following baseline variables were available and included in the multi-variate analysis: age, sex, race, ethnicity, systolic and diastolic BP, MAP, BMI, h/o diabetes, fasting glucose, A1c, and h/o cardiovascular disease, CRP, (CKD-EPI) eGFR, and ACR. P values ≤0.05 were considered significant.

Contrary to our hypothesis, higher endothelial NT expression associated with increased BA-FMD (β= 4.4; 95% C.I. 1.6,7.3; p value=0.003) when age, gender, race/ethnicity, SBP, BMI, h/o diabetes, and h/o cardiovascular disease, and CRP were included in the model. Higher NT expression correlated with decrease in NTG mediated dilation after adjusting for age, gender, race/ethnicity, SBP, BMI, h/o diabetes, and h/o cardiovascular disease, and CRP (β =-11; 95% C.I. -19, -2.2; p value=0.015). There was no significant correlation between NADPH oxidase and the outcome measurements of EDD or EID. Of note, we observed that age was a significant predictor of BA-FMD and NTG mediated dilation in unadjusted analysis and after adjusting for gender, BMI, SBP, glucose, and CRP (β= -0.11; 95% C.I -0.18, -0.04; p value=0.003). Further adjustment for NT but not NADPH oxidase attenuated this association (β for NT= -0.17; 95% C.I -0.31, -0.04; p value=0.014).

Endothelial expression of NT nor NADPH oxidase associated with endothelial dysfunction, but NT expression was associated with reduced EID. In addition, adjustment for endothelial NT expression attenuated the association between age and EDD suggesting that oxidative stress is mediator of age-associated endothelial dysfunction in CKD. That NADPH oxidase did not attenuate the association between age and EDD suggests that other pathways of oxidative stress mediate age-associated endothelial dysfunction in CKD.

Acceptance and Commitment Therapy Screening Model for Patients Undergoing Spinal Surgery

Student: Happy Kumar, M2
Mentor: Dr Catherine R Olinger, MD, University of Iowa Hospitals and Clinics Department of Orthopedic Surgery

**Background Information**

Chronic pain is an issue that affects over 100 million Americans daily. Acceptance and Commitment Therapy (ACT) has been found to be beneficial for patients with chronic pain by focusing provider efforts to teaching coping mechanisms for pain instead of eliminating the pain entirely. Data collected post-operatively indicates ACT benefits patients with 64.8% improving in at least one key domain in a longitudinal study by Vowles et al. 2011.

**Problem**

Presently the University of Iowa does not have a strict standard protocol for referring patients to ACT with the Department of Orthopedic Surgery Pain Psychologist.

**Methods**

Every patient that presented to spine clinic at University of Iowa Hospitals & Clinics (UIHC) from February 2022 to June 2022 was surveyed using the Pain Catastrophizing Scale (PCS). Patients indicated for spinal surgery were reviewed retrospectively. The patient list was filtered down to 600 adult spinal patients with pre-operative and post-operative PCS scores. 200 patients were chosen via a random number generator and additional information, such as the patients' History of Present Illness, Visual Analog Scale Scores, PROMIS-CAT Pain Interference Scores, and status of opiate usage were collected and presented to UIHC Orthopedic Spine Surgeons. Surgeons were blinded to the PCS Cutoff Scores. The UIHC Orthopedic Spine Surgeons then identified which patients they would indicate for ACT and their reasoning. Surgeon referral will then be compared to referral based on the PCS score of the same patients to evaluate the accuracy of the PCS scoring tool.

**Results**

Effectiveness of this screening tool will be based on frequency at which the surgeons and PCS score are complimentary. A department epidemiologist will assist in analysis of the data with the use of a ROC curve.

**Conclusion/Discussion**

The current goal for the study is to finish data analysis and determine PCS cutoffs. Using the PCS, a referral with the department pain psychologist would occur for patients that are deemed at-risk.

The goal following this study is to perform future investigations regarding PCS and ACT with patients regarding chronic opioid use and post-operative outcomes. Patients who were referred for help with chronic opiate use would be compared to PCS-referred patients and non-referred patients. Pre-operative ACT would be compared to patient outcomes post-operatively. The aim is to evaluate if PCS-referred patients have better pain management post-operatively as compared to the control and opiate-referred patients.

# Characterizing Patients Presenting with Chronic Scrotal Content Pain

**Lam J[1], Solsrud E[2], Moore A[3], Pearlman A[4]**

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Men with chronic scrotal content pain (CSCP) commonly present to various providers within the healthcare system. Despite its high prevalence, little research has been done to understand risk factors for the development of CSCP. In up to 50% of cases, the cause of pain is unknown and there are no widely accepted protocols for evaluation or management. The aim of our study was to characterize associated symptoms and concomitant concerns of those presenting with CSCP. Men presenting to a single urologist's office with CSCP were asked to complete a variety of questionnaires to assess their CSCP as well as urinary, sexual, musculoskeletal, and mental health. Questionnaires from 95 male patients were retrospectively reviewed. Our overall findings show a wide variety of presentations of CSCP. Patients commonly reported sexual health, urinary, and quality of life concerns. Nearly 68% of patients reported at least one hip symptom (HOOS, Jr.) and 61% reported low back pain interfering with daily life (Oswestry Low Back Pain Disability Questionnaire). Nearly a quarter of the patients qualified as having moderate to severe depression (PHQ-9) and 43% as having mild to severe anxiety (GAD-7). Our data suggest that men presenting with CSCP are complex. In order to create a personalized treatment plan, a more comprehensive understanding of these men is critical. Future studies should assess how directed interventions on associated symptoms impact CSCP management.

# Lesion mapping of depression in focal thalamic lesions

Molly JE Larson, Nicholas T Trapp, Joel E Bruss, Kai Hwang, and Aaron D Boes

## Background

Depression is the top cause of disability worldwide and the leading cause of disease burden in the US (Friedrich, 2017). Despite the ubiquity of depression, very little is understood about the anatomy and connectivity of the neural circuits involved. This creates a need for studies examining the structure and function of the neuroanatomical areas potentially involved in depression and mood disorders to better target diagnostics, interventions, and treatment. While there are many acknowledged lesions syndromes that result from thalamic damage, there is a lack of knowledge about the role of the thalamus in mood change.

Our group recently performed a large-scale lesion mapping study to examine risk and resilience networks in depression after brain lesions. We identified regions of the brain that, if lesioned, are associated with higher or lower depression symptom burden. This study points to the potential for personalized care and planning following brain lesions. However, one of the limitations of the study was lack of lesions in certain areas of the brain – including the thalamus. My project intends to help address this gap.

## Hypothesis

We hypothesized associations of depression "risk" and "resilience" networks can be determined via lesion mapping and lesion network mapping following focal thalamic lesions in human subjects.

## Method

Participants (n=25) with focal thalamic lesions were identified and recruited from the Iowa Lesion Registry, as well as via chart review of electronic medical records. Charts were reviewed to determine change in depressive symptoms before/after their lesion (symptoms n=12, no symptoms n=13). This included Beck Depression Inventory (BDI) or Geriatric Depression Scale (GDS) scores, diagnoses, medications, reports of patient conversations with clinicians, and family reports of patients' mood over time. Next, we identified lesion location and lesion mapped the MRI images of each person with a thalamic reference atlas, as well as ran lesion network mapping analyses.

## Results

Proportional subtraction analysis showed that lesions of the anterior, mediodorsal, and ventral anterior thalamus were associated with increased symptoms of depression. A multivariate lesion symptom map did not reach statistical significance.

## Discussion

Ongoing analyses are focused on evaluating lesion-associated networks. Qualitative analysis showed some association of regional anatomy in the thalamus and mood outcomes, but lack of adequate sample size and small anatomic area of interest make it difficult to achieve the resolution needed for more definitive conclusions.

**Title:** Use of novel biofoams to improve diabetic wound-healing

**Authors**
Student: Alexander Leach, M2; Faculty Mentor: James Byrne, MD, PhD

**Background**
Diabetes mellitus is one of the most diagnosed diseases worldwide. Financial repercussions resulting from sequelae of diabetes is estimated to account for $237 billion spent on direct medical costs and $90 billion lost in economic productivity in the United States alone (CDC). A major consequence of diabetes is impaired wound-healing and the development of chronic skin ulcers. This defect is attributable to multiple factors including reduced angiogenesis and granulation tissue deposition. Although current therapies including surgical debridement, wound dressings, antibacterial creams, and hyperbaric oxygen are efficacious, their cost-effectiveness is questionable. Additionally, many of these therapies remain logistical and financial obstacles for many patients. Several studies report the use of topical gases including carbon monoxide (CO) and oxygen ($O_2$) to have cytoprotective and anti-inflammatory effects (Takagi et al. 2022). Wound-healing is an oxygen-dependent process due to fibroblast proliferation and through the heme oxygenase pathway, CO possesses major immunomodulatory and anti-inflammatory properties, which have been demonstrated in HO-1 knockout mice. Given the enormous burden on healthcare systems worldwide, the development of a simpler, cost-effective treatment option warrants further investigation. We have developed a novel class of materials based upon molecular gastronomy, a field of the culinary arts, that can deliver gases in combination with other therapeutic agents to promote wound-healing. In this pilot study, we examined the use of topically applied gas-entrapping biofoams on cutaneous wounds, with the goal of transitioning to a diabetic mouse model.

**Purpose**
Formulate gas-entrapping biofoams comprised of growth and repair-promoting compounds that exhibit synergy with either CO or $O_2$ gas to reduce wound-healing time. Data from this project will be used to study improved wound-healing methods in a diabetic mouse model with the overall goal of developing an effective, low-cost treatment option for diabetic wounds.

**Methods**
Twenty 6-week-old male C57BL/6J mice were obtained from Jackson Laboratories and were divided into the following categories: no treatment (n=5), treatment with $N_2$ biofoams (n=5), treatment with $O_2$ biofoams (n=5), and treatment with CO biofoams (n=5). Dermal excisions of 6 mm were created on the dorsum of the animals. Wounds were isolated from the environment by affixing rubber devices onto the back of the mice. To create biofoams, solutions comprised of 0.5% by weight xanthan gum were transferred to whipping siphons which were charged to 200 parts-per-square-inch (PSI) with either $N_2$, $O_2$, or CO. Biofoams were topically administered directly onto the wounds consecutively for a total of 10 days. Images and measurements of the wounds were taken on the day of surgery (day 0), day 5, and day 10. Mice were sacrificed 10 days after creation of dermal wounds, and their wounds collected for histologic analysis. P-values were determined by one-way ANOVA with multiple comparisons.

**Results**
The wounds were visually inspected on days 0, 5, and 10, and wound size measurements were obtained at days 0, 5, and 10. Mice treated with $O_2$ and CO biofoams experienced an average 32% reduction in wound size at day 5 compared to 29% in control no treatment mice ($p=0.03$). On day 10, mice treated with $O_2$ and CO biofoams experienced an average 66% and 67% reduction in wound size compared to 64% in control mice ($p=0.04$). There was no difference in wound size between mice that received no treatment and $N_2$ biofoams.

**Discussion**
Mice receiving $O_2$ and CO biofoams had the largest reduction in wound size compared to our controls, which is in agreement with the previously demonstrated benefit by other gas-entrapping systems. Limitations to our studies include use of non-diabetic mice and a small magnitude of difference in wound-healing. To address these limitations, we plan to evaluate our novel materials in diabetic mice and also incorporate other wound-healing bioactive agents that may be synergistic activity with these gases.

2022 Medical School Research Conference
Grace Lee

# Lung Cancer Screening Program Adherence in a Tertiary Academic Center

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## Background

In 2011, the National Lung Screening Trial (NLST) demonstrated that lung cancer screening (LCS) with low-dose computed tomography (LDCT) reduces lung cancer mortality in a volunteer population aged 55 to 74 with at least 30 pack years of smoking history, leading the US Preventative Task Force to recommend LCS among high-risk individuals in 2014.[1,2] Notably, the NLST participants were 95% adherent to LCS and the simulation models that informed the screening guidelines assumed 100% adherence.[3] However, in non-research settings, the adherence rate may be closer to 55%.[4] A low adherence rate undermines the benefit of early cancer detection through LCS. In this study, we leverage the wealth of data from our institution's LCS program to investigate annual screening adherence rate at a centralized, tertiary academic center and across patient subgroups.

## Methods

We performed a retrospective electronic medical review of the University of Iowa's LCS program from 7/18 – 9/21. We captured data on: (1) patient characteristics (age; sex; race; primary insurance; smoking history, exposures; 6-year lung cancer risk per the $PLCO_{m2012}$ risk prediction model; nicotine dependence, measured by the Fagerstrom test), and (2) outcomes (initial screening results classified per Lung-RADS (LR); follow-up intervals; diagnostic evaluations and results). We identified a cohort with benign baseline screening results of either LR 1 or 2 who underwent initial LCS prior to 2/2/2021. Annual LDCT is recommended for these patients and we defined adherence as returning for imaging within 15 months after initial screening. Univariate and multivariable logistic regression models were used to test associations between co-variates and adherence with annual LCS.

## Results

From July 2018 to September 2021, a total of 620 patients participated in the LCS program and underwent screening, including 337 with initial screening results of LR 1 (n = 189) and LR 2 (n = 148) prior to 2/2/2021. The benign patient cohort mean age was 63.8 [SD 5.4] years, 46% were female, 94% were white, 23% had private insurance as the primary payer and 60% and 14% patients were Medicare and Medicaid beneficiaries, respectively. Family medicine/geriatrics clinic ordered the most LCS (n = 162, 48.1%), followed by the pulmonary clinic (n = 112; 33.2%) and general internal medicine (n = 60; 17.8%). Overall, 139 (73.5%) of LR 1 and 111 (75.0%) of LR 2 patients completed the annual repeat LDCT, respectively. We excluded 22 (9.2%) patients with repeat LDCT beyond 456 days from initial screening. Having Medicaid as the primary payer was associated with lower LCS adherence rate compared to the reference of private insurance (adjusted OR = 0.37, 95% CI = 0.15 – 0.92). Patients in the general internal medicine clinic versus family medicine/geriatrics clinic and higher number of tobacco pack years were associated with a lower LCS adherence rate on univariate analyses; however, the associations were not statistically significant after adjusting for co-variates. Patients who had delayed repeat LDCT were more likely to have a second scan with a higher LR classification than the baseline scan (unadjusted OR = 2.55, 95% CI = 1.00 – 6.23).

## Conclusion

At a tertiary academic center, the LCS adherence rate among patients who received benign initial screening results approximates – but is still lower than – the results of NLST in detecting early lung cancers. Medicaid beneficiaries were less likely to adhere to annual LCS.

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**Accuracy and Performance Characteristics of Administrative Codes for the Diagnosis of Autoinflammatory Syndromes: A Discovery and Validation Study**

Saeyun Lee, BA; Sujin Kim, PhD; Polly J. Ferguson, MD; Aleksander Lenert, MD, MS, FRCPC

**Introduction:** Autoinflammatory syndromes (AIS) are rare disorders of consistently activated innate immune system that results in uncontrolled inflammation of the body. Efforts to study AIS and address their debilitating impact on patients' quality of life have mostly been hampered by low disease prevalence of AIS. Recent studies have shown that AIS cases can be successfully identified and studied using administrative claims codes or International Classification of Diseases (ICD) in large health databases. However, there has been limited research regarding the accuracy and identification of the optimal codes for the diagnosis of AIS. In this study, we validate the accuracy of the 10$^{th}$ edition of the ICD or ICD-10 codes previously identified for the diagnosis of adult-onset Still's disease (AOSD), Behçet's disease (BD), and familial Mediterranean fever (FMF) and examine the performance characteristics of additional codes for the diagnosis of other AIS, including systemic juvenile idiopathic arthritis (SJIA), cryopyrin-associated periodic syndrome (CAPS), and synovitis, acne, pustulosis, hyperostosis, osteitis and chronic nonbacterial osteomyelitis syndrome (SAPHO-CNO).

**Objective**: To determine and validate the accuracy and performance characteristics of administrative codes for the diagnosis of AIS

**Methods**: Patients with potential AIS were identified from the University of Iowa Hospital and Clinic's electronic medical records using a screening filter comprised of the ICD-10 codes and interleukin-1 (IL-1) antagonists. Diagnostic criteria of AOSD, SJIA, BD, FMF, CAPS, and SAPHO-CNO were reviewed for each patient. Patients who did not meet the diagnostic criteria were categorized as non-AIS. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), and area under the receiver operating characteristic curve (AUC) of the ICD codes for diagnosing each AIS were calculated.

**Results**: Out of the 453 patients with potential AIS, 297 patients (65.6%) had a true AIS diagnosis. Sensitivity ranged from 73.91% (SAPHO-CNO) to 100% (BD, FMF) and PPV ranged from 15.63% (FMF) to 80% (CAPS). All AIS subtypes demonstrated high specificity, ranging from 81.51% (FMF) to 99.55% (CAPS) and high NPV, ranging from 98.18% (AOSD) to 100% (BD, FMF). All ICD codes or a combination of ICD codes for the diagnosis of specific AIS subtypes showed excellent AUCs (≥0.86).

**Conclusion:** This study validated the performance characteristics and accuracy of administrative codes for diagnosing AOSD, BD, and FMF, and examined novel codes for diagnosing SJIA, CAPS, and SAPHO-CNO. Administrative codes have high accuracy of identifying AIS patients and can be used to construct comprehensive AIS cohorts for clinical outcomes research.

**Endothelial TLR9 Inhibition via Targeted Nanoparticles Attenuates Radiation-Induced Blood-Brain Barrier Disruption and Cognitive Decline.**

Student: Nathanial R. Lindsey, Co-mentors: Karima Ait-Aissa, Isabella M. Grumbach

**Background:** Damage to neurovascular endothelium contributes to cognitive decline through increased blood-brain barrier (BBB) permeability. In our studies of mice and endothelial cells (ECs) subject to irradiation, we detect increases in mitochondrial reactive oxygen species ($_{mt}$ROS), mitochondrial DNA ($_{mt}$DNA) damage, and cell-free release of $_{mt}$DNA. Cell-free $_{mt}$DNA acts as a damage associated molecular pattern (DAMP), and similarly to bacterial DNA, binds Toll-like receptor 9, triggering a pro-inflammatory and pro-oxidative response. However, these irradiation-induced effects are attenuated with TLR9 inhibition or $_{mt}$ROS scavenging.
Our preliminary data implicate TLR9's critical role in propagating a feedforward mechanism of sustained oxidative endothelial damage and dysfunction following radiation therapy. We hypothesize that specific inhibition of TLR9 in neurovascular ECs during radiation will prevent BBB permeability and cognitive decline. Thus, the purpose of the study is to use a novel nanoparticle (NP)-based tool to examine the sequela of cranial irradiation and provide proof-of-concept for its use as a mitigator.

**Methods:** To target TLR9 in irradiated ECs, poly (lactic-co-glycolic acid)-based NP coated with cyclic Arg-Gly-Asp (cRGD)-peptide were designed and loaded with TLR9 antagonist (aTLR9, ODN-2088, 2.23ug/mg particle). cRGD-peptide is a ligand for integrin αvβ3, which is highly expressed in ECs post-irradiation (IR). C57Bl6 mice were administered NP-ODN-2088 (aTLR9-NP) or empty-NP (3mg injection) and subjected to unilateral X-ray cranial IR (dose = 12Gy). 30d post-IR, memory and learning ability were assessed with the Novel Object Recognition (NOR) and Y-maze tests. The functionality of nanoparticle treatment was assessed in vivo via BBB permeability, neuronal density, $_{mt}$DNA damage, and serum levels of $_{mt}$DNA; and in vitro via measurement of mtROS production and inflammatory markers in human brain microvascular endothelial cells (HBMECs) 120 hours post-IR (dose = 4Gy).

**Results:** In cultured HBMECs, treatment with aTLR9-NP prevented $_{mt}$ROS production 120 hours post-IR. This correlated with attenuated inflammatory intermediates (p65, TNFa, IL6, and IL8), as compared to treatment with vehicle. In mice, aTLR9-NP treatment preserved integrity of $_{mt}$DNA isolated from brain tissue and decreased blood levels of circulating cell-free $_{mt}$DNA. aTLR9-NP treatment showed protective effects on BBB permeability and neuronal dropout, and these findings corresponded with preserved cognition in both, NOR and Y-maze tests. aTLR9-NP treatment caused no changes in alkaline phosphatase, alanine transaminase, aspartate aminotransferase, or bilirubin levels, indicating no liver injury.

**Conclusion:** Inhibition of TLR9 in ECs was observed to prevent radiation-induced BBB permeability, neuronal dropout, and cognitive decline. Our findings support a pathway through which TLR9 links oxidative endothelial injury to neurological pathology. Currently there are no pharmacological options for treating radiation-induced normal tissue injury and targeting TLR9 poses a promising strategy.

**Incidence of Rapid Source Control Laparotomy (RSCL) Over Time and Impact on Patient Outcomes**

Connor P Littlefield BA, Maosong Ye PhD, Colette Galet PhD, Dionne Skeete MD

**Introduction:** The study purpose was to assess if the use of rapid source control laparotomy (RSCL) for emergent small bowel and/or colon surgery has changed over time with development of the acute care surgery specialty at our institution.

**Methods:** Adults admitted to our institution that were treated by general surgeons for emergent small bowel and/or colon surgery and selected to be entered in the NSQIP database were included. Overall, 906 patients admitted between 2006 and 2021 at our institution were included. The primary endpoint of this study was in-hospital mortality (IHM). Secondary endpoints included 30-day mortality, hospital length of stay (LOS), readmission, and discharge disposition.

**Results:** RSCL incidence increased from 11.8% to 20.7%. Our institution's IHM rate was 33.6% and 6.5% for RSCL and primary fascia closure (PFC) patients, respectively ($p < 0.001$). RSCL patients tended to be medically more complex over time ($p = 0.098$) and, although not significant, the mean age increased (42.9 to 60.4 years, $p = 0.104$). The percentage of patients with preoperative septic shock increased significantly (0.0% to 78.9%, $p < 0.001$) from 2006-2021. RSCL patients were more likely to have longer hospital LOS ($p < 0.001$), unplanned return to the OR ($p < 0.001$) and postoperative septic shock (OR = 1.030 [1.013-1.0460], $p < 0.001$). Stepwise binary logistic regression showed that our institution's IHM rates tended to decrease over time (OR = 0.944 [0.891-1.002], $p = 0.057$). Undergoing RSCL (OR = 4.255 [2.613-6.926], $p < 0.001$), being older (OR = 1.030 [1.013-1.046], $p < 0.001$) and frail (OR = 2.510 [1.378-4.575], $p = 0.003$), presenting with ascites (OR = 2.256 [1.103-4.612], $p = 0.26$), preoperative acute kidney injury (OR = 3.847 [1.855-7.979], $p <0.001$), and preoperative septic shock (OR = 3.486 [1.971-6.166], $p < 0.001$) were significantly associated with IHM.

**Conclusion:** The use of rapid source control laparotomy has increased over time. Despite a changing population with more older patients, patients with more medical complexity and more pre-operative septic shock, in-hospital mortality remained stable in patients who underwent RSCL. Future studies using the national data from the NSQIP database are warranted to assess whether the trend observed in in-hospital mortality rates at our institution is similar to that at the national level.

**Efficacy of Music Therapy for Hospice Patients with Premorbid Mental Health Diagnoses**

*Student*: Shana Liu, University of Iowa, Carver College of Medicine, M2
*Mentor*: Michelle Weckmann MD, University of Iowa, Departments of Family Medicine, Psychiatry, and Palliative Medicine

**Background:**
Music therapy is a widely used therapy for many conditions, including depressive and anxiety symptoms. Notably, there are no adverse effects associated with music therapy, making it a risk-averse treatment option that is well-tolerated by a majority of patients. While there is significant evidence demonstrating the efficacy of music therapy in psychiatric patients and hospice patients, there is little research exploring the efficacy of music therapy in patients exhibiting depressive and/or anxious symptoms who then enter a hospice or palliative setting. Previous research shows the extensive mortality gap between hospice patients with mental illness and those without, emphasizing the necessity for additional resources that providers can utilize while treating this population. Music therapy may be a novel opportunity to provide complementary treatment to improve the care of patients with mental illness at the end of life.

**Specific Aims:**
1. Determine whether music therapy is effective in decreasing depression and anxiety symptoms in hospice or palliative care patients with premorbid mental health conditions.
2. Gather qualitative evidence describing music therapy's impact on the patients' quality of life.

**Methods:**
Patients enrolled in the Iowa City Hospice or receiving care from the UIHC Supportive and Palliative Care team were approached for inclusion. All patients who had an anxiety or depression related diagnosis, were not comatose, and spoke English were eligible. Participants first completed pre-intervention PHQ-9 and GAD-7 screening tools. After 1-2 sessions of music therapy, depending on their existing care plan, participants completed the same post-intervention screening tools. The research team was unable to complete statistical analysis on the data. Results were quantified by subtracting the post-intervention score from the pre-intervention score. The qualitative portion consisted of semi-structured interviews with the patients' healthcare team to gather anecdotal opinions of music therapy in relation to patients' mental health symptoms and quality of life. Responses were transcribed in order to identify recurrent themes.

**Results:**
Due to difficulties with enrollment, only 2 participants completed the study. The average difference in GAD-7 scores was 2.5 and the average difference in PHQ-9 scores was 4.5. Four hospice team members, composed of 1 music therapist, 2 nurses, and 1 nursing assistant, were interviewed. The recurrent themes centered around (1) alleviation of anxiety and depression, (2) facilitation of difficult discussions, and (3) mood enhancement. In particular, each team member mentioned that patients seem calmer and happier after music therapy. Additionally, multiple providers emphasized how music therapy provided patients with a foundation to express difficult emotions regarding death and dying.

**Discussion:**
The patient population studied fell under multiple strict parameters. Due to the strain hospice patients are under, it was difficult to identify participants able to consent and complete the data screening tools. Additionally, one site was unable to facilitate research visits, so the pool of potential participants was further limited. Despite these limitations, the data is encouraging as each participant exhibited a decrease in both anxiety and depression. Furthermore, each hospice provider emphasized the benefits of music therapy that they have personally witnessed. Music therapy is an inexpensive, accessible, and non-invasive treatment that can be used to help vulnerable hospice patients who struggle with their mental health. The research team plans to continue gathering data from additional patients, including a control population that is not undergoing music therapy.

**Examining the role of the CB1 inverse agonist rimonabant in regulation of energy balance on different diets**

**Benjamin Linden, BA, Hussein Herz, Yi Chu, PhD, MS, Mohamad Mokadem, MD**

**Background:** Obesity is currently one of the most critical global public health crises. The etiology behind this obesity "pandemic" is not completely understood but it is thought to be multifactorial, including changes in diet, genetics, environment, stress, and behavioral components. For the presented research, the primary focus will be on diet. An unbalanced diet composition that is high in fat (specially saturated fats) and/ or simple carbohydrates (such as sucrose) has been implicated as one of the leading factors contributing to the growing epidemic of obesity in the United States. The Western diet is a common name for this diet. In previous studies, Western diet fed mice consumed larger quantities at faster rates while also eating more frequently when compared to standard diet fed mice. High fat diet has been shown to induce changes in the endocannabinoid system, specifically endocannabinoid -receptor 1 (CB1) within the small intestine. This change has been tied to promoting obesity by changing food intake behavior and by increasing fat absorption. Intestinal (or peripheral) CB1 signaling was also previously associated with facilitating hyperphagia. Blocking this receptor peripherally may offer a unique opportunity to control food intake, intestinal fat trafficking and sequentially induce weight gain without introducing the central psycho-neural effects of cannabinoids. Recent research has investigated the sympathetic nervous system and endocannabinoid signaling as potential controllers of the observed phenotype in high fat diet; the endocannabinoid system enhancing fat intake, and leptin driven sympathetic tone enhancing lipolysis. Other studies have shown similar effects with a conclusion that CB1 may be driving positive-feedback of fat consumption.

**Specific Aims/Hypothesis:** We intend to study the effect of CB1 inverse agonism on food intake, energy balance in mice on different diets- high-fat diet (HF), high-carbohydrate diet (HC), and regular chow (RC). Understanding the role of endogenous endocannabinoid signaling could allow for future development of personalized therapy for patients with obesity by selective manipulation of peripheral CB1 receptor function. We hypothesize that CB1 manipulation using Rimonabant (as inverse agonist) will have the most pronounced effect of decreased calorie consumption, browning of white adipose tissue, and weight loss in the HF diet compared to all the other groups.

**Methods:** We placed a group of 42 male mice on 3 types of diets at the age of 6 weeks: (1) a HF diet with 60% calories from fat (2) a HC diet, high sucrose diet (70% sucrose) and (3) a CHOW group. Mice were single housed. Mice were fed respective diets for 4 weeks to create the diet-induce obesity phenotype. Each diet group of 14 mice were divided and received either placebo or Rimonabant (a potent CB1 inverse agonist) by oral gavage at a dose of 10 mg/Kg. Mice were gavaged for 3 weeks. Weekly body weight, daily food intake during week 2, and body composition by NMR at time 0 and before sacrifice at week 3. Collection of several tissues including adipose tissues was performed. RT-PCR was performed on adipose tissue to further assess and compare browning, sympathetic activation, and lipolysis among the groups. Sections of adipose tissue were collected for IF staining.

**Results:** Only mice fed a HF diet had a decrease in average daily food intake when given rimonabant compared to their controls. All three diet groups lost weight relative to their controls when given rimonabant. Decrease in weight was HF- ~10%, HC- ~5%, RC-~6%, whereas both the HF and HC control mice increased in weight by around 3% from baseline. HF with rimonabant treated mice also had significant decrease in % body fat compared to control. HF and HC mice given rimonabant had a significant increase in UCP1 expression (by PCR and by IF staining) in mesenteric fat compared to their controls indicating browning of the adipose tissue. UCP1 was also increased in brown fat of only HC diet fed mice post- rimonabant but not on the other diets.

**Discussion/Conclusion:** Results of this study shows that administration of CB1 inverse agonist rimonabant causes a reduction in food intake in mice fed high fed diet; in addition, it induces increase in UCP1 (a marker of thermogenesis) only in mice fed high carb diet. However, rimonabant induces browning of mesenteric fat in mice fed either high fat or high carbohydrate diet. This synergistic effect leads to pronounced weight loss in both mice groups compared to mice fed normal chow. Our findings highlight a role of CB1 in mediating the energy homeostatic effects in weight loss. These findings support pursuing future opportunities to develop new targets for management of obesity at the molecular and/or physiologic levels. Rimonabant previously failed as a potential drug therapy for obesity due to its neuro-psychiatric side effects. Nonetheless, the above-mentioned findings suggest an intriguing role of peripheral CB1 in food intake regulation. A better understanding of the signaling pathways underlying the endocannabinoid-mediated regulation of energy balance could possibly lead to a targeted pharmacotherapy for treatment of obesity.

# Infectious Dermatologic Disease Diagnosed Through Teledermatology Platform in Tanzania

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*These authors contributed equally to this work.

**Background**:

Bagamoyo, Tanzania is located in east Africa and faces a shortage of healthcare specialists, especially dermatologists. In 2017, a pilot study identified the need for dermatologic care in the Bagamoyo district, and further research assessed the effectiveness of a secure teledermatology platform in providing dermatologic consults and enhancing care. Infectious diseases are a large part of the disease burden in low-income countries and tropical regions and can manifest as disorders of the skin. Therefore, knowledge of the prevalence and treatment of these diseases is important to further inform diagnostic approaches and treatment pathways and interventions to improve the health of patients.

**Purpose:**

This study aimed to evaluate the prevalence of infectious dermatologic disease diagnoses out of the total cases reported on the teledermatology platform and summarize the most common treatments prescribed for the infectious cases. We hypothesized that skin infections were common in the community, despite difficulty in obtaining confirmatory tests.

**Methods:**

Using the secure teledermatology platform (africa.telederm.org), deidentified dermatologic patient cases were uploaded by local primary care physicians in Tanzania. Cases included patient demographics and history, lesion images, and the local provider's initial diagnosis and treatment. Dermatologists in the United States then consulted on the cases by providing a specialist diagnosis, recommended treatment plan, and any specialist feedback regarding the diagnostic or treatment process for enhancing local provider education. The teledermatology cases were consolidated, categorized, and analyzed in Microsoft Excel. Descriptive statistics were used to describe the infectious disease diagnoses given and treatments instituted.

**Results:**

Out of 186 total patient cases evaluated through the teledermatology platform, there were 277 total dermatologic diagnoses. Infectious dermatologic diseases comprised 136 out of the 277 diagnoses (49.10%). Infections fell into 1 of 4 categories: (1) bacterial, (2) viral, (3) fungal, and (4) parasitic. Out of 68 total bacterial infections, bullous impetigo was the most common with 23 diagnoses (33.82%). There were 6 total viral infections, 3 herpes simplex virus diagnoses and 3 varicella zoster virus diagnoses. Of the 34 fungal infections, tinea versicolor was the most common (18 diagnoses, or 52.94%). There were 28 parasitic infections, all of which were scabies.

Treatments recommended depended on the etiology. For the majority of cases, topical medications were prescribed (mupirocin ointment, clotrimazole cream, and lindane lotion). For viral infections, the antiviral acyclovir was used most often. Diagnoses were limited by lack of culture data and confirmation tests available.

**Conclusion:**

Infectious diseases constitute a large portion of the dermatologic burden as supported by the teledermatology cases reviewed here. For treatment of the diseases, topical medications were most commonly recommended, which may be related to the cutaneous nature of the diseases, but also could be secondary to a limited drug formulary for dermatologic conditions. Future goals resulting from this study include improving patient education initiatives and establishing community outreach regarding prevention of contraction and spread of infectious diseases. Further evaluation of the drug formulary available also could be done to expand the availability of oral therapies to help reduce the prevalence and subsequent spread of the infectious diseases.

# THREE-DIMENSIONAL WEIGHT BEARING CT DISTANCE AND COVERAGE MAPPING ASSESSMENT OF HALLUX VALGUS DEFORMITY. A CASE-CONTROL STUDY.

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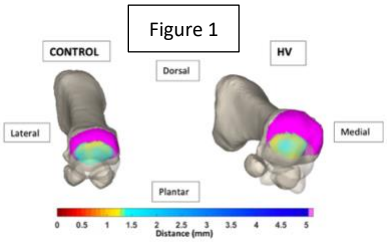
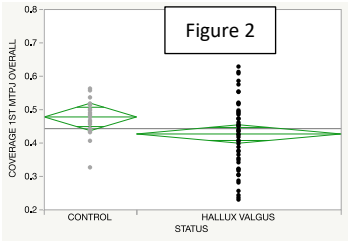
**Background:** Hallux valgus (HV), popularly termed as bunion, is a common progressive deformity of the entire forefoot, mainly characterized by a three-dimensional (3D) distortion involving varus, dorsiflexion, and pronation of the first metatarsal, valgus deformity of the hallux, and lateral subluxation of the sesamoids. Weight-bearing CT (WBCT) images allow for a reliable 3D assessment of the deformity as well as an accurate evaluation of 1st metatarsophalangeal joint (MTPJ) morphology. Using WBCT images, 3D distance maps (DM) can be generated, assessing thousands of distance measures and relative positioning between opposing bones and joint surfaces. The distribution of joint distances between opposing articular surfaces can then be characterized using color-coded maps, or coverage maps (CM), to highlight areas of adequate joint interaction or joint subluxation. The data and images provided by this analysis can improve the ease of interpretation of the spatial relationship of the 1st MTPJ as well as support the identification of arthritic degeneration and related symptoms, which may influence treatment outcomes of HV.

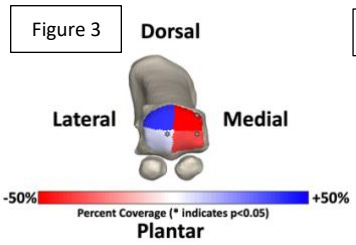
**Purpose/Hypothesis:** The aim of this study was to develop a 3D WBCT DM and CM algorithm to evaluate the 1st MTPJ and 1st metatarsal-sesamoid joint interactions in patients with HV and controls. Our hypothesis was that patients with HV deformity would demonstrate significant lateral subluxation of the 1st MTPJ as well as lateral subluxation of the first metatarso-sesamoid articulations.

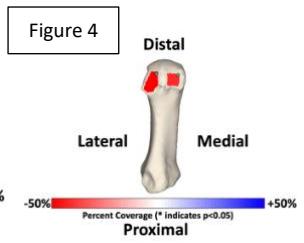
**Methods:** In this IRB-approved retrospective case-control study, we included 51 feet from patients with HV who underwent a WBCT of the affected foot and 54 feet from healthy controls. Disior Bonelogic® 2.0 was utilized to semiautomatically segment and create models of all bones in the foot and ankle, and these models were analyzed in MatLab code (Mathworks Inc., Natick, MA, USA). These models were exported as triangulated surface models and smoothed using Geomagic Design X (Artec 3D, Luxembourg) to remove any bone surface irregularities. Distance mapping was then performed to determine the boundaries of the 1st MTPJ and metatarso-sesamoid joints, including the articular surfaces of the 1st metatarsal head, medial and lateral sesamoids, hallux proximal phalanx and inter-sesamoid crista. The surfaces of the 1st MTPJ were divided into two-by-two grids using the principal component analysis (PCA) of principal axis of the joint surface to provide a more detailed analysis. Distance maps were then color-coded to highlight areas of adequate joint interaction (blue), impingement/arthritis (red), and subluxation (pink). Blue regions represented expected distances in joint interaction, ranging from 1 to 5 mm; distances from 0 to 1mm were colored yellow/red representing proximity of the articular surfaces, consistent with arthritis/impingement; regions with distances > 5 mm were represented in pink, with no opposing articular facet, consistent with subluxation. Normality of the DM data was analyzed using the Shapiro-Wilk test. DM value comparisons between HV and control patients were performed using paired t-tests or paired Wilcoxon. P-values of less than 0.05 were considered statistically significant.

**Results:** Example color-coded coverage maps for an HV patient and a control are demonstrated in Figure 1. In the comparison of 1st MTPJ coverage, HV patients demonstrated significantly decreased overall coverage (42.7%, Confidence Interval [CI] 39.9% to 45.4%) in comparison to controls (47.8%, CI 43.7% to 51.9%) (Figure 2), with an overall relative decrease in 1st MTPJ coverage of 14.7% ($p<0.001$). When assessing the 1st MTPJ quadrants, articular coverage was significantly higher in HV patients for the plantarlateral quadrant (HV 88.6% vs. 78% Controls, $p=0.0009$) and significantly decreased in both the dorsomedial (HV 8.8% vs. 19.7% Controls, $p<0.0001$) and plantarmedial quadrants in HV patients (HV 46.2% vs. 74.9% Controls, $p<0.0001$), consistent with plantarlateral subluxation of the hallux in the 1st MTPJ and medial-dorsal deviation of the 1st metatarsal. No significant changes were noted in the articular coverage of the dorsolateral aspect of the 1st MTP joint. Significant changes in the articular coverage of the metatarso-sesamoid articulation were also noted when comparing HV and controls, with average medial and lateral sesamoid coverage of respectively 31.1% and 22.6% in HV patients, and 58.4% and 52.9% in controls ($p<0.0001$). Figures 3 and 4 illustrate the relative percentage change in coverages between HV patients and controls, with blue colors representing areas of relative increased coverage and red colors representing areas of relative decreased coverage in HV patients when compared to controls.




**Conclusions:** In this study, we developed a WBCT distance and coverage map algorithm to assess 3D joint interaction, articular coverage, and subluxation in patients with HV. We observed significant 1st MTPJ subluxation in HV patients when compared to controls, as well as significant metatarso-sesamoid joint subluxation in both medial and lateral sesamoid articulations, with apparent medial and dorsal deviation of the 1st metatarsal, lateral and plantar deviation of the hallux proximal phalanx and lateral subluxation of the sesamoids. We hope that WBCT 3D distance and coverage maps can optimize the efficiency and accuracy of diagnosis, staging, treatment of HV patients, potentially improving outcomes in HV deformity. Further prospective studies and outcome studies are needed.

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# Analyzing molecular profiles and clinical responses of patients with clear cell renal cell carcinoma: a retrospective study

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**Background**: Clear cell renal cell carcinoma (ccRCC) is the 6th most common cancer in men, the 9th most common cancer in women, and the most common malignancy of the kidney in the United States. Until less than a decade ago, best practices for treating ccRCC involved nephrectomy alone. In recent years, however, therapies for ccRCC shifted from the use of immunotherapies to anti-angiogenic drugs in combination with nephrectomy, and it is our current clinical understanding that this combination leads to better outcomes.

**Objective**: In this two-phase retrospective study, we aim to conduct both a laboratory and clinical investigation of 50 patients diagnosed with renal cell carcinoma. In our laboratory investigation, we aimed to analyze differences in the expression of TGF-β, PD-L1, and VEGF between ccRCC tumors with and without sarcomatoid differentiation. In our clinical investigation, our goal was to analyze differences in clinical outcomes between ccRCC patients treated with nephrectomy alone versus those treated with the nephrectomy and systemic treatment combination.

**Patients and Methods**: We first extracted clinical information from the charts of 50 patients diagnosed with ccRCC at the University of Iowa Hospitals and Clinics. This information included age, sex, BSA, baseline IMDC risk score (range 0-3), date of diagnosis, nephrectomy date, nephrectomy type, additional therapies, and clinical response throughout the course of their treatment. Responses were categorized into complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). CR and PR represent favorable outcomes, while SD and PD are unfavorable. We then retrieved information regarding the expression levels of TGF-β, PD-L1, and VEGF from each patient's cancer. In our laboratory investigation, we measured and compared levels of TGF-β, PD-L1, and VEGF, stratifying by histological subtype of ccRCC. In our clinical investigation, we analyzed the efficacy of treatment via nephrectomy alone versus the nephrectomy and systemic therapy combination by comparing differences in rates of survival with no evidence of disease (CR) between the two groups. Lastly, we stratified our patients by IMDC risk score and analyzed survival rates again.

**Results**: Of our 50 patients, 47 were diagnosed with a form of clear cell renal cell carcinoma. Of those 47, 4 were described to have tumors with sarcomatoid differentiation, and 43 were non-sarcomatoid. Our study found higher levels of TGF-β and lower levels of PD-L1 in tumors with sarcomatoid differentiation compared to tumors without sarcomatoid differentiation. There was no significant difference in VEGF levels. Following clinical investigation, our study found that the addition of systemic therapy led to better outcomes after 24 months, measured as a proportion of patients with no evidence of disease. The addition of systemic therapy also had a greater impact on outcomes in patients with higher IMDC scores (difference of -55.97% at IMDC 0 versus +8.89% at IMDC 2 at 3 months post-treatment).

**Clinical Implications**: Though our limited sample size prevents us from drawing definitive conclusions, we must still draw attention to trends seen in our 50-patient retrospective study. First, we now have greater evidence that the biomarker profiles of ccRCC tumors with or without sarcomatoid differentiation are different, meaning that clinicians must take the extra step of classifying their patients' tumors before selecting the appropriate systemic therapy, in order to achieve an optimal response for their patients. Second, we have greater evidence to support the idea that we must stratify patients by their IMDC risk score when conducting any analyses, and when choosing treatment regimens, particularly when deciding upon the addition of systemic therapy. We hope that both findings will encourage clinicians to take a personalized medicine approach to their treatment of ccRCC and ultimately improve outcomes in their patients.

**Efficacy of Intralesional Steroid Injections in the Treatment of Cutaneous Lymphoma: Experience at an Academic Medical Center and Review**

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Intralesional corticosteroid injections have long been utilized as a treatment method for cutaneous lymphomas, but their use and efficacy are not well-defined. In recent years, these have been included in the consensus guidelines for the treatment of cutaneous B-cell lymphoma published by the World Health Organization-European Organization for Research and Treatment of Cancer (EORTC), but the literature review on which this specific guideline was based did not include any cases describing its use. Due to the heterogeneity and relative rarity of primary cutaneous lymphomas, controlled clinical trials in their treatment have been almost nonexistent.

At present, a limited number of case reports and small, single-institution retrospective reviews have been reported but sufficient evidence remains lacking. We conducted a review of outcomes at the University of Iowa Hospitals and Clinics in patients with diagnosed cases of primary B-cell and T-cell cutaneous lymphomas undergoing intralesional triamcinolone injections to provide evidence for its validity as a therapy, which has not been widely reported in the literature thus far. The University of Iowa Cutaneous Lymphoma Registry served as a starting point for this data collection, with additional individual chart review. The patient population was sub-divided into those diagnosed with cutaneous B-cell lymphoma and those diagnosed with cutaneous T-cell lymphomas. For each group, we analyzed patient outcomes, specifically remission of disease and relapse, to determine the efficacy of the proposed treatment. We also analyzed for differences in treatment outcomes correlated to patient demographics, disease stage, anatomic location, and dosage. Lastly, we conducted a systematic review of existing literature in this area to provide more comprehensive and generalizable assessment of this treatment method.

# A Retrospective Review of Trends in Return to Sport (RTS) Following Anterior Cruciate Ligament (ACL) Reconstruction in Athletes

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**Background:** ACL tears commonly occur among athletes, especially women, and reinjuries happen often. More research has been conducted on hamstring tendon (HT) and bone-patellar tendon-bone (BPTB) grafts than quadriceps tendon (QT) grafts. There is a lack of evidence concerning the impact of graft choice on RTS rates. QT autografts may cause less anterior knee pain than BPTB autografts. HT grafts have shown to pass RTS testing sooner and have higher re-tear rates. Additionally, RTS following revision ACL reconstruction has shown to be more difficult.

**Purpose:** To determine whether QT autografts have superior RTS results when compared to HT and BPTB autografts and to evaluate RTS data following primary and revision ACL reconstruction in athletes.

**Hypothesis:** Recovery following ACL reconstruction is quicker with QT autografts than HT and BPTB autografts.

**Methods:** Recreational and competitive athletes ages 13-24 from 2010-2022 that underwent primary or revision ACL reconstruction at the University of Iowa were included. There were 837 total athletes comprised of 341 HT, 358 BPTB, and 138 QT autografts, of which 729 were primary and 108 were revision surgeries. RTS rates, RTS testing results, clearance time, and reinjury rates were gathered. RTS testing data included isokinetic testing quadricep and hamstring muscles and jump testing results. A Kruskal-Wallis test was used to detect differences among continuous variables. A GLIMMIX model was used for continuous variables to adjust for age and activity level. Chi-square statistics and Fishers exact test were used for categorical variables. An odds ratio, adjusted odds ratio, and 95% confidence intervals were provided by logistic regression. Statistical significance was measured at $p<0.05$.

**Results:** The median ages were 18 for HT and BPTB and 17 for QT ($p= 0.0001$). Females were 50.73% of HT, 42.86% of BPTB, and 41.30% of QT grafts. 118/130 (90.77%) HT, 124/136 (91.18%) BPTB, and 39/52 (75.00%) QT returned to previous level of play ($p=0.0045$); BPTB remained statistically more likely to return to previous level of play than QT after adjusting for age and activity level. 28/341 (8.21%) of HT, 142/358 (39.66%) BPTB, and 80/138 (57.97%) QT completed RTS testing ($p<0.001$); after adjusting for age and activity level, the results remained significant. Median isokinetic quadriceps testing at 300 degrees per second was 92% for 26 HT athletes, 83% for 134 BPTB athletes, and 87% for 77 QT athletes ($p= 0.0006$); results remained significant following age and activity level adjustment. ACL retear rates were 12.02% for HT, 3.07% for BPTB, and 5.07% for QT ($p<0.0001$) with hamstring remaining significantly more likely to suffer an ACL retear after adjusting for age and activity level.

The median ages were 17 and 19 for primary and revision reconstruction, respectively ($p=0.0004$). Females comprised 46.02% and 44.44% of subjects in primary and revision reconstructions, respectively. 256/284 (90.14%) primary and 25/34 (73.53%) revision reconstructions returned to previous level of play ($p=0.009$); these results held after adjusting for age and activity level. 16/729 (2.19%) primary and 37/108 (34.26%) revision reconstructions had lateral extra-articular tenodesis (LET) performed ($p<0.0001$); after adjusting for age and activity level, these results remained statistically significant. Median clearance time was 28.65 weeks for primary and 34.69 weeks for revision reconstruction ($p=0.0013$). ACL retear rates among primary and revision reconstructions were 7.41% and 4.63%, respectively ($p=0.2926$).

**Conclusions:** QT and revision reconstructions were less likely to return to previous level of play, while QT was more likely to undergo RTS testing. BPTB athletes demonstrated less quadriceps strength on isokinetic testing at 300 degrees per second. Clearance took about 6 weeks longer for revision reconstructions. HT athletes were more likely to suffer a subsequent ACL tear.

**Evaluating Hypotension as a Predictor of Cardiovascular Physiology in Preterm Infants**

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Mentor: Danielle Rios, MD, MS – Stead Family Department of Pediatrics

**Background:** Hypotension is diagnosed in approximately 50% of very-low-birth weight infants during their hospitalization. Despite its frequency, there is not a universally accepted definition of hypotension for this patient population. Many definitions of hypotension have been proposed; however, none of these definitions are based on cardiovascular physiology. Because of the lack of consistency in defining hypotension, NICUs vary in their approaches to treatment. Hypotension in premature infants has been associated with adverse outcomes; however, treatments for hypotension also carry risks. The relationship between infants with hypotension or those being treated for hypotension and abnormal cardiovascular physiology has not been investigated.

**Purpose:** The aim of this study was to evaluate blood pressure as a predictor of cardiovascular health in infants born less than 27 weeks gestational age (GA) while considering the cardiovascular treatments received by the patients. We hypothesized that blood pressure will be a poor predictor of cardiovascular health in preterm infants at 24 hours of life.

**Methods:** A retrospective cohort study was conducted of premature infants born < 27 weeks GA ($\leq 26^{+6}$) who were admitted to the NICU at the University of Iowa Stead Family Children's Hospital (11/2018-5/2022). Those with life threatening congenital anomalies or anatomic cardiac disease other than PDA, patent foramen ovale/atrial septal defect or small (<1mm) muscular ventricular septal defect and those without targeted neonatal echocardiography (TnECHO) performed within the first 24 hours were excluded. Cardiovascular physiologies were compared between patients who were hypotensive without treatment, normotensive without treatment, and those who received treatment for hypotension. Hypotension was defined as a mean blood pressure less than GA in weeks or a systolic BP and/or diastolic BP less than the 3rd percentile for gestational age. ANOVA was used to analyze demographics, clinical characteristics, hourly blood pressures, and TnECHO findings according to group. Blood pressure trends according to group were analyzed using generalized estimating equations. The p-value was set at 0.05. Potential abnormal cardiovascular physiologies included hemodynamically significant patent ductus arteriosus (hsPDA), acute pulmonary hypertension, left ventricular dysfunction, right ventricular dysfunction, biventricular dysfunction, and sepsis or volume depletion.

**Results:** 170 patients met eligibility criteria. Of these patients, 114 were normotensive (67%), 24 were hypotensive (14%), and 32 had received treatment for hypotension (19%). The neonates who were hypotensive or treated for hypotension had a lower gestational age at birth (p=0.024) and a lower birth weight (p=0.003). Despite the low frequency of hypotension, 103 patients (61%) had abnormal cardiovascular physiology on TnECHO in the first 24 hours of life. Hemodynamically significant patent ductus arteriosus was the most common abnormal physiology in each group. No significant difference in cardiovascular physiology was found between the three groups.

**Conclusion/Discussion:** Abnormal cardiovascular physiology is seen is over half of preterm infants within 24 hours after birth, regardless of blood pressure patterns or cardiovascular treatments.

# SEQUENTIAL INTRAVESICAL GEMCITABINE AND DOCETAXEL VERSUS BACILLUS CALMETTE–GUÉRIN FOR THE TREATMENT OF HIGH-RISK NON-MUSCLE INVASIVE BLADDER CANCER: A RETROSPECTIVE COMPARISON OVER A DECADE

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**Introduction**

Bacillus Calmette-Guerin (BCG) is currently recommended as adjuvant treatment following complete transurethral resection of bladder tumor for high-risk non-muscle invasive bladder cancer (NMIBC) and has been shown to be superior to single-agent chemotherapy regimens. Initially utilized due to ongoing BCG shortages, intravesical gemcitabine and docetaxel (Gem/Doce) has been increasingly utilized at our institution as first-line therapy. We aimed to compare, over an overlapping time period, the oncologic outcomes of patients with high-risk treatment-naïve NMIBC treated with Gem/Doce versus BCG as a first-line adjuvant therapy.

**Methods**

We retrospectively identified 312 patients with high-risk treatment naïve NMIBC treated at our institution between January 2011 through December 2021; 174 treated with BCG and 138 treated with Gem/Doce. After complete TURBT, patients received a 6 weekly induction regimen of either sequential intravesical gemcitabine (1 gram) and docetaxel (37.5 mg) or 1 vial of BCG (with or without 50 million units of IFNα-2b). Maintenance regimens were initiated if disease free at first follow-up. The Primary outcomes was high-grade recurrence-free survival (HG-RFS). Survival probabilities were estimated and plotted using the Kaplan-Meier method. Cox regression models were used to evaluate the effect of patient, disease, and treatment characteristics on outcomes. Adverse events were reported using CTCAE v5.

**Results**

Median follow-up for patients receiving BCG and Gem/Doce was 49 and 23 months, respectively. Pre-treatment stage was similar between patients receiving BCG and Gem/Doce (p=0.46). Other baseline characteristics including gender, smoking status, tumor size, and multifocality were similar between groups (all p>0.05). RFS estimates at 6, 12, and 24 months were 72%, 67%, and 62% in the BCG group and 90%, 83%, and 78% in the Gem/Doce group, respectively (Figure 1). On multivariable Cox regression analyses controlling for age, gender, treatment year, and presence of CIS, Gem/Doce treatment was associated with superior RFS (HR 0.56, p=0.02) and HG-RFS (HR 0.57, p=0.04) compared to BCG (Table 1). PFS was 97% at 2-years for Gem/Doce versus 92% for BCG (p=0.02); however, CFS and CSS were not statistically different (both p=0.06). Induction with BCG was associated with greater treatment discontinuation rates than induction with Gem/Doce (9.2% versus 2.9%, p=0.02).

**Conclusions**

Gem/Doce is a reasonable alternative treatment for high-risk NMIBC in the setting of the BCG shortage. These data provide benchmark outcomes to support ongoing prospective single-arm and randomized studies of these agents, to further clarify the role of Gem/Doce as a first-line treatment.

**Perceptions about Clinical Trials and Barriers to Participation among Black and Hispanic Patients.**

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***Introduction:*** Black and Hispanic people make up about 35% of the US population yet represent only 6% of patients enrolled in clinical trials. Due to this severe underrepresentation, racial/ethnic minorities are often excluded from receiving potentially beneficial therapies. Thus, we sought to investigate perceptions about clinical trials and barriers to participation among Black and Hispanic patients in Iowa. We hypothesized that perceptions and barriers varied along race/ethnic identity, age, gender, and distance from a hospital.

***Methods:*** Adult patients who self-identified as Black or Hispanic in their medical record and underwent in-person evaluation at surgery clinics of a major tertiary care center in Iowa between May 2021 and August 2022 were invited to participate in the study (IRB#:202101150). A previously validated survey was used to assess patients' awareness about clinical trials, their recruitment preferences, and their perceptions about research integrity. Chi-square or Fisher exact test was used to compare proportions where applicable, and $p < 0.05$ was considered statistically significant.

***Results:*** Of 144 patients approached, 87(60%) completed the survey. Of these, 85 (98%) were appropriate for inclusion in the final analyses. Majority were Black (58%), age <50 (56%), male (58%), and lived >30miles from a hospital (54%). Overall, only 3.5% described ever participating in a clinical trial even though 49% indicated interest in participating in a trial. Lack of information about clinical trials was the most common barrier cited and 82% were unaware of online information about clinical trials. Furthermore, 54% were dissatisfied with the current information they had about clinical trials. Majority (67%) expected their physicians to inform them about clinical trials, and many found it appropriate to be contacted by mail (56%) about trials more than by phone (50%). In the subgroup analyses, statistically significant differences included: Black patients being more likely to perceive pharmaceutical sponsored trials as having a conflict of interest (52% *Vs* 29% Hispanic); Hispanic patients being more likely to report work schedule as the strongest barrier to participation in trials (18% *Vs* 4% Black); ≥50-year-old being less likely to trust that their privacy would be protected (41% *Vs* 17% for <50 years); those who lived >30miles from a hospital being more likely to report distance as the strongest barrier to participation in trials (29% *Vs* 3% for <30 miles) and less likely to find randomization acceptable (65% *Vs* 36% for <30miles). There were no significant differences found between male and female gender.

***Conclusion:*** Increasing the representation of Black and Hispanic patients in clinical trials is integral in ensuring health equity. However, despite interest in participating in clinical trials, Black and Hispanic patients frequently lack adequate information. Moreover, perceptions about clinical trials and barriers to participation vary along demographic factors of race/ethnic identity, age, and distance from the hospital. Addressing these perceptions and barriers may increase participation in clinical trials by Black and Hispanic patients.

**Screening of Acquired Long QT-Prolonging Drugs in Induced Pluripotent Cardiac Stem Cells Reveals Trafficking Defects in HERG**

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**Background**

Mutations in $K_v11.1$ (HERG) cause inherited long QT syndrome (LQTS) type 2 by disrupting channel function or membrane trafficking. Acquired LQTS is caused by drug binding to HERG and directly blocking the channel pore, reducing $I_{Kr}$ and prolonging QTc in persons with decreased repolarization reserve. Alternatively, these drugs could bind to HERG and interfere with trafficking, reducing the number of HERG channels at the membrane.

**Objective**

We sought to understand the effects of known acquired LQTS-causing drugs from various classes (terfenadine, haloperidol, ondansetron, fluconazole, azithromycin) on HERG trafficking within HEK293 cells and human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs).

**Methods**

HEK293 cells stably expressing HERG (HERG-HEK293) and hiPSC-CMs were cultured in varying concentrations of selected drugs for 24 hours and 48 hours, respectively. Differences in trafficking were identified by immunoblot comparing the terminally-glycosylated HERG at 155 kD and the immature core-glycosylated HERG at 135 kD. In HEK293 cells, the mutant HERG-G601S and HERG-HEK293 cells treated with 100 $\mu$M arsenic trioxide ($As_2O_3$) served as trafficking-deficient controls. In hiPSC-CMs, cells treated for 48 hours with $As_2O_3$ served as trafficking-deficient controls.

**Results**

HERG-HEK293 cells treated with haloperidol ($\geq$50 $\mu$M) demonstrated a decrease in the size of the terminally glycosylated band, appearing at 140-145 kD in comparison to the fully glycosylated 155 kD (Fig. 1A). HERG-HEK293 cells treated with terfenadine ($\geq$15 $\mu$M) demonstrated a deficiency in terminal glycosylation (Fig. 1B). Ondansetron, fluconazole, and azithromycin treatments at 1, 10, and 100 $\mu$M demonstrated no effect on the fully glycosylated band in HERG-HEK293 cells. In hiPSC-CMs, cells treated with azithromycin and haloperidol demonstrated a deficiency in terminal glycosylation (Fig. 1C). Cells treated with terfenadine demonstrate a deficiency in both core and glycosylated HERG bands

**Conclusions**

Haloperidol administration altered terminal glycosylation of HERG in HEK293 cells and decreased the amount of terminally glycosylated HERG in hiPS-CMs. Terfenadine administration decreased the amount of terminally glycosylated HERG in HEK293 cells and the amounts of both core and terminally glycosylated HERG in hiPS-CMs. Azithromycin treatment, on the other hand, decreased the amount of terminally glycosylated HERG only in hiPS-CMs. Together, these data suggest that changes in trafficking, a non-pore blocking mechanism, may underlie some cases of acquired LQTS. In addition, differences in ion channel trafficking machinery in HEK293 cells compared to hiPS-CMs may limit their utility for the study of acquired long QT-associated drugs.

**Protein Biomarkers as Independent Predictors of Prognosis and Clinicopathologic Outcomes in Oral Cavity Squamous Cell Carcinoma**

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## Objective

A cohort of oral cavity squamous cell carcinoma (OCSCC) cases were analyzed with several protein biomarkers in conjunction with clinicopathologic and surgical margin data to determine if any biomarkers act as independent predictors of (1) disease specific or recurrence free survival, (2) recurrence in "good prognosis" patients with negative surgical margins or no nodal disease, or (3) the presence of positive surgical margins or nodal disease.

## Subjects and Methods

This study included 145 patients with OCSCC treated with surgery between 2005 and 2014 at University of Iowa Hospitals & Clinics. An OCSCC tissue microarray (TMA) was created using 145 tumors. Emphasis was placed on selecting tumors with positive or close intraoperative margins, tumors associated with nodal disease, and tumors which were expected to have a favorable prognosis based on negative surgical margins or no nodal disease, but the patient experienced recurrence. The TMA was analyzed using six protein biomarkers including Survivin, Snail, Cyclin-D1, Matrix Metallopeptidase 7 (MMP7), P16, and Epidermal Growth Factor Receptor (EGFR). Protein biomarker positivity and clinicopathologic data were analyzed with particular emphasis on whether any biomarker was able to predict disease specific survival, recurrence free survival, recurrence in patients with negative margins or no nodal disease, presence of a positive surgical margin, or the presence of nodal disease.

## Results

OCSCC TMA slides were stained with biomarkers, which were scored based on previously described methods in the literature. Significant clinicopathologic predictors for decreased disease pecific survival included nodal disease, perineural and lymphovascular invasion, and positive/very close (<1 mm) margins. On univariate analysis of 145 TMA patients, disease specific survival was negatively impacted by Survivin positivity (HR 1.93, p-value 0.04). Recurrence free survival was negatively impacted by EGFR and Cyclin-D1 positivity (HR 1.61, p-value 0.05; and HR 2.19, p-value 0.04, respectively). MMP7 presence conferred improved recurrence free survival (HR 0.81, p-value <0.01). Thirty-six "good prognosis" (negative margins, no nodal disease) patients who ultimately experienced a recurrence were identified in the TMA. No protein biomarker was able to predict recurrence in this patient group. Looking at primary tumor characteristics, EGFR positivity conferred an increased risk of positive/close margins (OR 2.01 p-value 0.04). No biomarker was able to significantly predict nodal involvement, although Cyclin-D1 positivity trended toward significance.

## Conclusion:

Associating protein biomarkers with clinicopathologic characteristics in OCSCC analysis is a novel technique for more accurately predicting outcomes and prognosis. TMAs may be used to assist in high-throughput analysis of biomarkers in order to discover significant associations. In this cohort of 145 patients, Survivin, EGFR, and Cyclin-D1 positivity trended toward decreased survival; MMP7 conferred improved recurrence free survival. Among 36 patients who experienced a recurrence despite initial "good prognosis" surgical characteristics, no biomarker was able to predict recurrence, however this is a small patient cohort. EGFR positivity was found to confer an increased risk of having a positive/close surgical margin. Moving forward, it is important to continue analysis of large numbers of patient samples in order to extract meaningful biomarker data to help with prognosis and outcome predictions.

# A latent class analysis of spatial accessibility to maternity care services in Pennsylvania

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**Objective:** To characterize spatial accessibility to maternity care services in Pennsylvania using a latent class analysis.

**Methods:** We included all Pennsylvania-residing patients in Pennsylvania birth records from 2011-2015. Patients were categorized into latent classes using the following spatial indicators of maternity care service accessibility: number of obstetricians and maternity hospitals in a 15 km radius, and distance to the nearest obstetrician, maternity hospital, and level 3 neonatal intensive care unit (NICU). The number of latent classes were determined using Bayesian information criterion (BIC).

**Results:** We classified the spatial accessibility to maternity care services of 679,767 patients into 2-5 groups. We used 5 groups based on BIC classified as very high, high, medium, low, and very low. In the very high group, patients had an average of 355 obstetricians and 11 maternity hospitals in a 15 km radius. They had to travel 1.8 km to the nearest obstetrician, 3.8 km to the nearest maternity hospital, and 4.2 km to the nearest level 3 NICU. In the very low group, patients had an average of 1 obstetrician and 0 maternity hospitals in a 15 km radius. They had to travel 18.7 km to the nearest obstetrician, 26.7 km to the nearest maternity hospital, and 56.9 km to the nearest level 3 NICU.

**Conclusion:** These findings suggest that patients with varying spatial accessibility to maternity care services may be categorized into distinct profiles. Future analyses will explore whether spatial accessibility latent classes are associated with adverse maternal and infant perinatal outcomes.

**Title:** The Evaluation of 3D and Augmented Reality Models in Teaching of Congenital Heart Diseases

**Name:** Ashray Mohan
**Mentor's name:** Ravi Ashwath, MD
**Other collaborators:** Krista Young, MD

**Abstract:**

**Background:**
3D cardiac models in printed and digital forms have been shown to be an effective tool for patient and staff education regarding the anatomy of congenital heart diseases. However, accessing these models in a practical and efficient way remains a challenge. A possible solution may lie in the use of 3D cardiac models which are accessible via quick response (QR) codes.

**Purpose of study:**
This study aimed to test whether having access to 3D cardiac models, as a supplement to CT interpretations, enhanced knowledge and understanding of subjects regarding a complex congenital heart defect. Additionally, the study aimed to evaluate the ease-of-use of QR codes as a means of accessing and manipulating the 3D cardiac models.

**Methods:**
An educational module on total anomalous pulmonary venous return (TAPVR) was created using CT generated 3D models, which were made accessible via QR codes. Nine multiple choice questions tested knowledge and understanding of TAPVR among medical students, trainees, and staff when presented with clinical cases with and without the 3D model. A pre- and post-test included Likert-like questions (1-10 scale) for subjects to rate their understanding of cardiac, aortic arch, and TAPVR anatomy. The post-test also included 6 questions for subjects to rate their opinion (1 disagree-10 agree) on the utility of the 3D models and QR codes.

**Results:**
A total of 60 subjects participated in the study. Subjects scored significantly better on the knowledge questions when they had access to the 3D models (median increase: 2.5; IQR: 1.0-4.0; $p<0.0001$). There was a significant increase on the pre- versus post-test self-rated understanding of TAPVR anatomy (median increase: 2; IQR: 0-2; $p<0.0001$). All 6 post-questions about the utility of 3D models and ease of use of QR codes had a favorable (6-10) rating from at least 85% of participants.

**Conclusions:**
QR codes were shown to be an easy way to access 3D cardiac models. Further, having access to the models significantly improved objective knowledge scores and self-rated understanding of a complex anatomical defect. Future research will assess the utility and ease of use of QR codes in the healthcare setting for patient education and clinical care.

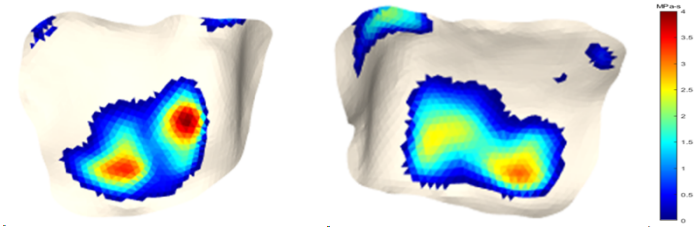
**Initial Evaluation of Contact Stress Alterations in Patients with Non-Articular Ankle Fractures**

**Student**: Bryan Mouser, M2
**Mentor**: Jason Wilken, Department of Physical Therapy and Rehabilitation
**Other Collaborators:** Don Anderson, Cesar de Cesar Netto

**Background:** Arthritis of the ankle is a unique entity compared to arthritis affecting other joints, with most cases (78%) being directly attributable to joint trauma. The major factors responsible for the development of post-traumatic osteoarthritis (PTOA) involve the degree of acute chondrocyte damage at the time of injury and altered joint loading conditions that result in a more chronic type of chondrocyte damage. Abnormal joint loading can be caused by a variety of factors. High-energy ankle fractures that involve the articular surface can result in gross incongruities of the tibial plafond, leading to measurable alterations in contact stresses that have high concordance with PTOA development. While ankle PTOA develops at a higher rate after articular ankle fractures, non-articular ankle fractures can also lead to PTOA. Elevated contact stresses have been hypothesized to play an important role in ankle PTOA development for these cases but have not yet been demonstrated in real patients. The purpose of this study is to determine if ankle contact stresses are elevated following non-articular ankle fractures using a validated discrete element analysis model.

**Methods:** Patients with existing weight-bearing CT scans were reviewed. 8 patients were identified that suffered an ankle fracture that did not involve the tibial plafond, did not have clinical or radiographic evidence of OA at the time of CT scan, and had a bilateral scan available with an uninjured contralateral lower limb. Normative gait data gathered using Vicon motion capture software were applied to an OpenSim musculoskeletal model and scaled for each patient. Tibial and talar geometries from WBCT scans were applied to a discrete element model and used to calculate tibiotalar contact stress exposure of the tibial surface over 13 instances during the stance phase of gait.

**Results:** To date, contact stress analysis has been completed for four of the eight total patients. Three patients suffered supination-external rotation ankle fractures (two on the right side, one on the left side), and one patients suffered a pronation-external rotation fracture on the right side. For all patients, peak contact stresses were elevated in the injured extremity compared to the noninjured extremity by an average of 1.478 MPa-s (.51, .85, 2.77, and 1.78). Total tibial surface contact area exceeding 2 MPa-s of stress were also increased for each injured ankle by an average of 15% (14%, 5%, 26%, and 15%).



Right Tibia (injured) Left Tibia (uninjured)

**Discussion:** Review of the initial results of this contact stress analysis has demonstrated elevations in tibiotalar contact stress on the side of non-articular ankle fracture compared to control limb for all four cases. While non-articular ankle fractures do not result in obvious joint surface incongruities as fractures affecting the tibial pilon do, they still result in measurable alterations in model contact stress. These changes are most likely attributable to ligamentous injury associated with rotational ankle fractures. Excessive external rotation was identified in the fracture mechanism for all four patients, which has been linked consistently to deltoid ligament and ankle syndesmotic injuries. Both the deltoid ligament and ankle syndesmosis play a significant role in maintaining the alignment of the tibia and talus during weightbearing, and even subtle shifts in alignment can alter contact stresses significantly. While these injuries may not result in anatomical incongruities significant enough to be seen on radiographs, the high sensitivity of the OpenSim model to tibiotalar alignment (up to just tenths of a millimeter) allows the detection of minor misalignment that can cause the changes in contact stress demonstrated in this study. The results of this study do not allow for any conclusions regarding the threshold of contact stress that is tolerable before PTOA develops, but they do support theories that tibiotalar contact stress plays an important role in PTOA development for non-articular ankle fractures.

**Platelet-Rich Plasma Injection for the Treatment of Stress Urinary Incontinence in Females: A Randomized Placebo-Controlled Study**

Medical Student: Hannah Nakatsuka
Principal Investigator: Annah Vollstedt, MD
Collaborators: Elizabeth Takacs, MD, Karl Kreder, MD, Joseph Kowalski, MD, Kimberly Kenne, MD, Catherine Bradley, MD, Leah Ashton, MD, Colin Johnson, MD

**Background:** Stress urinary incontinence (SUI) is the unintentional loss of urine from increasing intra-abdominal pressure due to physical exertion, coughing, or sneezing. If conservative therapies fail, there are more invasive management plans, which come with greater risk complications, including voiding dysfunction, injury to neighboring organs, hemorrhage, and possible mesh complications. Platelet-Rich Plasma (PRP) injection concentrates one's own platelets accelerate the healing of injured tendons, ligaments, muscles, and joints. PRP has been studied in the treatment of musculoskeletal injuries and emerging data suggest that PRP may be used as a potential minimally invasive therapy for SUI in females.

**Purpose:** The primary aim of the study is to determine the safety and the 6-month post-treatment efficacy of PRP injection in the treatment of female SUI.

**Method:** This is a single blind, randomized controlled trial comparing the efficacy of 5 mL PRP injection into the anterior vaginal wall to a 5 mL injection of sterile saline for the treatment of SUI. Participants are females 18 years and older with stress-predominant urinary incontinence, evaluated through the Medical, Epidemiologic, and Social Aspects of Aging Questionnaire, and a positive cough stress test at the baseline visit. Visual analog scale (VAS) for pain related to the procedure was collected after the injection. Adverse events were recorded. Patients are followed at 1, 3, and 6-month intervals after injection. Responses to the Incontinence Quality of Life Questionnaire, Questionnaire for Urinary Incontinence Diagnosis, Female Sexual Function Index, and Patient Global Impression of Improvement are collected at 1, 3, and 6-month intervals. Treatment success of PRP is defined as a negative cough stress test and a Perception of Global Improvement score of "very much better" or "much better." Statistical analysis will be completed at the end of the 6-month intervals for all participants.

**Results:** A total of 24 participants have undergone randomized and injection of either PRP or the saline placebo. Target enrollment is a total of 50 participants. The mean VAS score of pain during the procedure was 2.0/10 for active treatment participants (range 0-5) and 3.5/10 (range 1-8) for the placebo group. A total of 15 participants have reached the 1-month interval. Adverse events at the 1-month interval included urinary tract infection (1/15), vaginal spotting (1/15), vaginal discomfort (1/15), and persistent vaginal pain (1/15).

**Conclusion**: Injections of PRP into the anterior vaginal wall for the treatment of SUI appear to be well-tolerated and safe in this randomized controlled trial. Enrollment is ongoing.

# Effects of COVID-19 on Protein C Activation

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**Introduction**: Thrombosis is a common complication of COVID-19 but the mechanisms by which SARS-CoV-2 infection affects prothrombotic and antithrombotic pathways are poorly understood. We tested the hypothesis that COVID-19 impairs the protein C (PC) antithrombotic pathway via histone-dependent inhibition of thrombomodulin (TM) activity.

**Methods**: TM-dependent activation of PC was measured using a two-stage assay. In the first stage, 1.0 μM human PC, 10.4 nM human alpha-thrombin, and human TM (hTM) (derived from lung lysate) or 16 nM recombinant rabbit TM (rTM) were incubated for 30 min at 37°C with plasma from COVID-19 patients or healthy subjects, histone H3, or citrullinated histone H3 (H3Cit), with or without a histone inhibitory aptamer (KU7, 1μM). In the second stage, PC activation was measured spectrophotometrically using the chromogenic substrate S-2366. Data are mean ± SEM; *p*-values were determined by one-way and two-way analysis of variance (ANOVA).

**Results:** Since extracellular histones are increased in COVID-19 plasma, we first examined whether histones or citrullinated histones have an inhibitory effect on PC activation. We found that H3 decreased PC activation with rTM from 14.9 ± 1.3 to 2.7 ± 0.4 units/μg protein ($p<0.001$) and tended to decrease with hTM from 2.3 ± 0.1 to 1.3 ± 0.1 Units/μg protein ($p=0.110$). In contrast, no inhibition was observed with H3Cit. These data suggest that the charge difference between H3 and H3Cit may differentially affect PC activation. Next, we examined whether COVID-19 plasma alters PC activation compared to healthy plasma. We observed that COVID-19 plasma decreased PC activation with rTM (70.5 ± 1.2 to 51.6 ± 4.4 units/μg protein ($p=0.031$), but there was no effect of healthy plasma (70.5 ± 1.2 vs 63.9 ± 3.2 units/ug protein, $p=0.89$). Selectively neutralizing histones with KU7 did not change the inhibitory effect of COVID-19 patient plasma on PC activation (healthy plasma: 63.9 ± 3.2 vs 58.6± 5.9 units/μg protein, $p=0.940$; COVID-19 plasma: 51.6 ± 4.4 vs 47.2 ± 5.4 units/μg protein, $p=0.940$), suggesting a histone-independent mechanism.

**Conclusions:** (1) PC activation is decreased by extracellular histones but not citrullinated histones. (2) Plasma from COVID-19 patients inhibits PC activation via a histone-independent mechanism.

**Major Histocompatibility Complex (MHC) Genotyping in Domestic Ferrets to Investigate MHC Mismatch and Development of Chronic Lung Allograft Dysfunction**

**Student:** Natalie Nguyen, M1
**Mentors:** Kalpaj R. Parekh, MBBS, FACS, Thomas J. Lynch, PhD

## I. Background

Approximately 50% of patients receiving lung transplants develop chronic lung allograft dysfunction (CLAD) within 5 years. Since there is no effective treatment for CLAD, transplantation is the only viable therapeutic option. Domestic ferrets have shown to be a reliable model to investigate CLAD pathogenesis in an orthotopic model of lung transplantation. This model exhibits the full spectrum of inflammatory and fibrotic pathology seen in CLAD, with long-term survivors also displaying lesions that histologically match those seen in humans. However, ferret transplantation studies have been limited by the lack of information about Major Histocompatibility complex (MHC) antigens to strategically select individuals for transplant which can help favor certain transplant injuries for further investigation. With more information on different ferret MHC haplogroups, we can strategically utilize mismatched pairs to optimize the probability of CLAD development post-transplant.

The development of divergent CLAD pathologies is affected by various immunologic mechanisms. Antibody-mediated rejection (AMR) is one of the risk factors for CLAD pathogenesis. AMR causes damage to the allografts by the production and circulation of donor-specific antibodies (DSA) against donor MHC. We aim to develop an assay to identify ferret MHC mismatch that will aid as a research tool to predict post-transplant outcomes such as CLAD development and time to develop an injury.

## II. Method

Five HLA genes (DQA2, DQB1, DOB, DRA, DMB) were amplified, cloned, and sequenced from 38 archival domestic ferret tissues. 18 samples were from 9 transplantation pairs with known post-transplant outcomes. The process consisted of extracting total RNA from spleen or peripheral blood mononuclear cells, synthesizing cDNA, and finally using designed primers to amplify HLA genes. PCR products were sequenced by Sanger dideoxy method and analyzed using alignment software to identify polymorphisms that resulted in divergent amino acids sequences.

## III. Findings

HLA-DQA2, HLA-DOB, HLA-DRA, and HLA-DMB genes each were found to have two distinctive haplotypes (A, B) while HLA-DQB1 had three haplotypes (A, B, C). We also observed a substantial number of animals expressing mixed haplotypes, from 25% of animals expressing mix AB and BC in HLA-DQB1 to up to 53% expressing mix AB in HLA-DOB.

Seven lung transplant donor-recipient pairs were sequenced for HLA mismatch. Three recipients had histologic and radiographic findings consistent with obliterative bronchiolitis (OB) – the obstructive phenotype of CLAD - at the time of sacrifice, while four recipients had no evidence of CLAD. The average time from transplant to sacrifice was 209 days, with no significant difference between the groups ($p=0.46$). The average recipient with OB had 2.33 haplotype mismatches compared to 0.25 mismatches in the no CLAD animals ($p=0.047$). All donor-recipient pairs that developed OB had at least one mismatch and all recipients with the disease were mismatched at HLA-DQB1. One donor-recipient pair that did not develop CLAD had one mismatch (HLA-DQA2).

In conclusion, mismatch in HLA haplotypes does contribute to the development of CLAD in the ferret. Among five HLA genes that were sequenced and analyzed, HLA-DQB1 was shown to have the strongest impact on the development of OB.

Abstract: Student: Jack Ohringer Mentor:

Mental Healthcare Gaps and Highlights from the Perspective of a New Critical Access Mental Health Care Center in Iowa City

From January to May of 2022, eight narratives were collected from mental health workers working in a range of fields at GuideLink, a new critical access mental health center in Iowa City, Iowa. These narratives were collected with the intention of providing qualitative information that can help GuideLink identify ways to improve, communicate to funders on the benefits of the organization, and share with peer organizations to improve health and well-being nationwide. GuideLink opened its doors in January 2021 and is one of three critical mental health access centers in the state of Iowa. It is also the only access center in the state that combines a detoxification unit, crisis stabilization unit, and sobering unit under the same roof. These services are housed together to facilitate the treatment of patients with complex needs who may benefit from multiple, or all services during their visit. Narratives were collected from the executive director, a peer support specialist, multiple detoxification unit nurses, a detoxification assistant, a triage counselor, a paramedic, and another administrator. Thematic analysis of these narratives was conducted to identify the most common themes that were discussed in these narratives. Themes that arose in four or more of the narratives that highlighted positive attributes of GuideLink included: partnership with community organizations, offering collaborative services, client-centered care, short waitlists compared to local hospitals, jail/emergency room diversion, easing of the burden of care for patients with complex needs, and prioritization of staff needs and well-being. Themes also addressed gaps in our mental health care system including: a lack of resources dedicated to treating chronic mental illness, lack of short-term and low-barrier housing, stigma that prevents patients from seeking care and funders from supporting mental health care more actively, and high caseloads for clinicians. Narratives further highlighted recommendations to improve GuideLink and other peer organizations by suggesting that a campus of even more services should be created (including residential detoxification, short-term housing, assistive outreach programming, more peer support specialists, and more spiritual/religious adversaries). In Iowa City, ambulances are not currently allowed to drop off at GuideLink due to its classification as an urgent care center, so it has also been recommended to modify this local policy. In conclusion, this analysis identified many positive attributes of GuideLink and areas for improvement in our mental health care system and within GuideLink itself. Looking forward, GuideLink hopes to expand its services and act on many of the recommendations made by the staff. In the future, more quantitative analysis of GuideLink should be done to assess its impact on the local community and additional areas for improvement. The themes addressed by four or more of the narratives include (consider breaking this into gaps vs highlights (for the benefit of other organizations hoping to learn from GuideLink)): the ability to treat chronic mental illness is a gap in our system, outreach to community organizations and collaborative services offered by GuideLink are valued, local hospitals struggle with mental health crises and often have long waitlists which is challenging for patients, the emergency room and jail diversion provided by GuideLink is valued, there is a desire to expand GuideLink services to include a campus of services, nighttime/weekend services, residential detoxification services, and assistive outreach programming, employees appreciate that their needs are prioritized at GuideLink, lack of housing is a major gap in Iowa City and there is a desperate need for more low-barrier short term housing, the fluidity of processes at GuideLink is valued and eases the burden of care for patients with complex needs, client-centered care at GuideLink is valued, there is a need for more staffing at GuideLink, and stigma is still a major gap in the mental health care system. There were also important themes only mentioned by those who could speak directly to them. Those include: there is a lack of resources to treat patients experiencing paranoias and acute crises are a gap in our system, high caseloads cause significant strain on providers, there need to be more detoxification units in Iowa, there is a need for more peer support specialists and spiritual/religious adversaries in the field, gratitude expressed by patients at GuideLink makes the work meaningful, ambulances need to be allowed to drop off patients at GuideLink, the “upstream” care that GuideLink provides is more cost effective than emergency care at a hospital, and the sobering unit is highly valued by the community, especially since it is a college town.

# Menstrual Hormone-Induced Cyclic Thumb CMC Instability and Degeneration in Women: A Systematic Review

**Student: Emily Parker**
**Mentor: Joseph Buckwalter V, Orthopedics and Rehabilitation**

## Introduction

Relaxin is a hormone which peaks during the luteal phase of the menstrual cycle, and a known collagenolytic promoter that has been shown to avidly bind tissues supporting the trapeziometacarpal (TMC) joint in women. We hypothesize a causal linkage between cyclic binding of relaxin to the supporting tissues of the female TMC joint and the early-onset, severe TMC joint osteoarthritis (OA) commonly seen in women.

## Materials and Methods

A systematic literature review was performed per PRISMA guidelines, qualitatively and quantitatively assessing papers regarding relaxin-TMC joint stability interactions. The primary outcome variable was TMC joint degeneration/loss of function; the late consequences of relaxin-induced instability. The secondary outcome variable was early symptoms of relaxin-induced instability, namely asymptomatic TMC joint laxity in young women.

## Results

In healthy young women, menstrual cycle peak relaxin levels corresponded with asymptomatic TMC joint instability. Immunohistochemical studies of TMC joint arthroplasty patients showed avidly increased relaxin binding around the TMC joint in women but not men. Demographic analysis of patients from the TMC joint arthroplasty studies show a predominantly female cohort, who were on average significantly younger than the male surgical patients.

## Conclusions

Each relaxin peak during the menstrual cycle signals receptors on the soft tissues supporting the TMC joint, including—critically—the main stabilizing ligament: the anterior oblique. The cyclic instability is typically asymptomatic for years after menarche, but causes cumulative chondral microtrauma. This likely causes the early-onset, high severity TMC joint OA clinically pervasive among female patients seen in orthopedic hand clinics. Further research is indicated to develop risk assessment strategies and potential interventional options.

# An OR Crash Course for Medical Students: the effect of a simulation training session on self-perceived preparedness for surgical rotations

Parks S, Steffen H, Lence T, Fleishhacker Z, Shaffer S, Vandenbosch N

**Background:** A small number of studies have highlighted that medical students tend to feel their training in both surgery and obstetrics & gynecology is below average, and it has been found that poor practical skills training is a major factor causing operating room student stress in the clinical environment. Furthermore, research demonstrates that a considerable proportion of perioperative staff find medical students to be lacking in knowledge about OR sterility and scrubbing procedures. This data suggests suboptimal preparation of medical students for their role as a member of a surgical team. It is generally accepted that simulation-based training improves medical students' skills in clinical settings**.** A pilot simulation activity was created to introduce University of Iowa medical students on their surgery or OB/Gyn clerkships to issues relating to patient safety, infection control, and practical skills.

**Objective:** To explore the effect of practical skills training on medical students' confidence and feelings of preparedness to be safe and effective members of the surgical team.

**Methods:** This orientation session takes place prior to general surgery and obstetrics & gynecology rotation operative experiences and addresses the need for students to practice roles they will perform while participating in patient care. The simulation allows students to practice scenarios including safe patient transfer, manipulation of equipment such as arm boards or stirrups, scrubbing, donning sterile garb, navigating a sterile field, and foley catheter placement. Using a retrospective pre-post design, a survey was sent to students following the orientation asking them to self-assess their skills and knowledge using a 5-point Likert scale.

**Results:** 58 out of 104 students (55.8%) responded to the survey. Students reported the session helped them better understand how they could be helpful and involved members of a surgical team. They also felt significantly more prepared for the operating room than prior to the session. Furthermore, students reported significantly increased confidence in their ability to scrub with minimal guidance, don sterile garb, maintain a sterile field and identify breaks in sterility, safely assist with patient transfer, and manipulate basic OR equipment ($p < 0.00001$).

**Discussion:** Patient safety is of utmost importance in the operating room and this orientation fills a current gap in students' practical knowledge as they prepare to enter their surgical clerkships. Providing medical students with the skills and confidence needed to be safe and effective members of the surgical team prior to entering the operating room is of benefit to the team, students, and patients. Our conclusion is that medical education programs should include hands-on practical skills education as part of their surgical clerkship curriculums.

# Disparities in depression treatment and monitoring in primary care patients

David Bedell MD, Meghal Patel M1

**Introduction:** Mental health care has become an increasing burden on the US healthcare system, with a lack of access to care driving the issue. Consequently, most patients seek mental health care from their primary care provider. However, previous studies have shown disparities in mental health screenings and treatment amongst primary care patients based on age, gender, race, and language spoken.

**Objective:** To determine PHQ-9 administration rates and treatment disparities amongst adult patients diagnosed with depression seen in primary care at UIHC.

**Methods:** This was a retrospective chart review. Initial data from was collected by the IT team for patients with a diagnosis of depression seen between 2019 and 2022 at UIHC. The patients were then included for analysis if they were 18 years old or older, seen at a family medicine or internal medicine clinic, depression was first noted in their chart in 2019, and they were not being seen by behavioral health. Statistical analysis was conducted on the 2191 patients included using SPSS software to discern differences in PHQ-9 administration and pharmacological treatment based on gender, gender conformity, race, ethnicity, age, and language spoken. Chi square and linear association were used where appropriate, with an alpha of 0.05.

**Results:** Approximately 55 percent of patients included for data analysis did not have a PHQ-9 score recorded in the appropriate field in EPIC. Gender non-conforming individuals were less likely to be on psychiatric medications than gender conforming individuals ($p<.001$). Increasing age was associated with increased likelihood of being prescribed psychiatric medications and decreased likelihood of having a PHQ-9 score recorded ($p=.003$ and $p<.001$, respectively). There were no statistically significant differences in treatment with psychiatric medications or having a PHQ-9 score recorded based on ethnicity or primary spoken language. While there was no difference in treatment with psychiatric medications based on biological sex, male patients were less likely to have a PHQ-9 score recorded than female patients ($p<.001$).

**Conclusions:** Documenting PHQ-9 scores in patient charts on Epic could be a potential area for improvement. Further analysis is warranted to determine potential causes but may include verbal screenings that are not recorded in the appropriate field or documentation in only in the written note. The significantly lower percentage of males having a PHQ-9 score recorded compared to females aligns with other studies that have shown males are less likely to be diagnosed with depression but have a higher burden of unmet mental health need. Increasing age was associated with a higher likelihood of being on psychiatric medications, yet the PHQ-9 scores tended to decrease in severity. This may be due to patients continuing medications started prior to obtaining a diagnosis from UIHC or due to clinician perspective on psychiatric treatment for the elderly.

**Automated Quantification of Hemorrhage Volume to Predict Complications of Aneurysm Rupture**

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[1]University of Iowa, Carver College of Medicine
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**Introduction:** Aneurysmal subarachnoid hemorrhage (aSAH) has a mortality of 35%. Among those who survive, many are left with disability and cognitive dysfunction. The Fisher score is currently used clinically to evaluate the degree of aSAH. However, the Fisher score is subjective and has limited accuracy in predicting complications of aSAH, such as vasospasm and hydrocephalus. The volume of hemorrhage may more accurately predict complications of aSAH.

**Hypothesis:** Volume of hemorrhage can accurately predict complications of aSAH.

**Methods:** Only patients with saccular aneurysms and a noncontract head CT scan on presentation with a Fisher score $\geq 2$ were included in this retrospective study. For these patients, the following medical complications were recorded: vasospasm, hydrocephalus, and need for permanent ventriculoperitoneal (VP) shunt. Aneurysm size was defined as the largest diameter. The volume of aSAH hemorrhage was measured using a custom automated image-processing algorithm that utilized region-growing and 3D k-means clustering. The algorithm was validated by comparison to the average of two independent raters who manually measured the volume of hemorrhage by drawing regions of interest. Patients who died within seven days of presentation were excluded from analysis of vasospasm and VP shunt placement. Logistic regression and ROC analysis were performed to evaluate the association between blood volume and clinical outcomes. Spearman's correlation was calculated to evaluate the association between aneurysm size and volume of hemorrhage.

**Results:** The volume of hemorrhage was measured in 141 total patients. The algorithm was validated using ten patients. The manual measurements of aSAH were highly similar between raters (ICC = 0.988, $p < 0.001$, 95% CI 0.911-0.997). Algorithmic measurements of aSAH were highly correlated with manual measurements (ICC = 0.966, $p < 0.001$, 95% CI 0.852-0.992). The mean difference between the algorithmic measurements and manual measurements was -3.14 mL. Hemorrhage volume was associated with development of vasospasm (OR = 1.03, $p < 0.001$, 95% CI 1.01-1.05), hydrocephalus (OR = 1.08, $p < 0.001$, 95% CI 1.04-1.14), and need for permanent VP shunt (OR = 1.03, $p = 0.006$, 95% CI 1.01-1.05). Hemorrhage volume predicted the development of vasospasm (AUC = 0.692), hydrocephalus (AUC = 0.775), and need for permanent VP shunt (AUC = 0.669). Hemorrhage volume was not correlated with aneurysm size ($p = 0.65$).

**Conclusion:** We developed and validated a fully automatic algorithm that accurately measured the volume of hemorrhage following aneurysm rupture. Patients with larger volume of hemorrhage were more likely to develop vasospasm, hydrocephalus, and need a permanent VP shunt. Quantification of hemorrhage volume may be useful for medical management of aSAH patients by identifying those at higher risk for developing complications.

**Periarticular Local Infiltrative Anesthesia Compared to Interscalene Block in Arthroscopic Rotator Cuff and Labrum Repair**

**Authors:** Jacob Peake, Steven Leary MD, Robert Westermann MD, Brian Wolf MD

**Background:**
The interscalene nerve block (ISB) is the currently most used method for post-op analgesia in arthroscopic shoulder surgeries. However, there are known complications to this method including rebound pain after hospital discharge and transient to chronic neurologic complications. Periarticular local infiltrative anesthesia (LIA) is an increasingly popular option to manage post-operative pain in a variety of orthopedic surgeries. The combination of long-acting anesthetics, opioids, and NSAIDs has shown equivalent pain control and reduced opioid use compared to ISB in shoulder arthroplasty. Similarly, the use of a long-acting anesthetic periarticular injection alone has also been shown to offer comparable pain levels to ISB after arthroscopic rotator cuff repair. However, there is still a paucity of literature directly comparing regional anesthesia to LIA in arthroscopic shoulder procedures such as rotator cuff and labrum repair.

**Purpose:**
The aim of this study is to compare postoperative pain and recovery after shoulder arthroscopy in patients who received a regional anesthesia with ISB or LIA. We hypothesize that patients who receive LIA have similar post-op analgesic effects to those who receive ISB.

**Methods:**
We performed a retrospective review of a prospectively collected registry of patients who underwent arthroscopic rotator cuff or labral repair at the University of Iowa within the last 10 years. All patients received either an ISB or LIA for immediate postoperative pain relief. Patients who received an alternative or trial nerve block were excluded, as well as patients whose surgery transitioned from an arthroscopic to open repair. Patients who did not received ISB or LIA, as well as those who did not receive a repair were excluded. The primary outcomes of interest are visual analog scale (VAS) pain levels and milligram morphine equivalents (MME) consumed post-operatively. Demographic variables collected included age, sex, body mass index (BMI), race, and smoking status. Surgical data collected included the number of anchors placed and concomitant procedures performed.

**Results:**
A total of 2,458 records were reviewed, of which 1,987 (1,542 rotator cuff and 445 labrum) met inclusion criteria. Of the 1,542 rotator cuff repairs, 292 (18.9%) received LIA. These patient's post-op VAS scores (4.58) were statistically higher than those who received ISB (1.83, $p<0.001$). Their post-op MME consumed (35.86 mg) was also significantly higher than the ISB receiving patients (15.34 mg, $p<0.001$).

Of the 445 labrum repairs, 231 (51.9%) received LIA. These patient's post-op VAS scores (3.76) were significantly higher than those who received ISB (1.34, $p<0.001$). Their post-op MME consumed (26.71 mg) was also significantly higher than those receiving ISB (11.02 mg, $p<0.001$).

**Discussion:**
In the primary outcomes measured (post-op VAS pain levels and MME consumed) patients receiving LIA had less post-op analgesia after rotator cuff and labrum repair surgeries when compared to patients who received ISB. This research provides evidence that LIA does not provide equal analgesia for patients receiving rotator cuff or labrum repairs. Our research is ongoing, and further data is being collected to compare follow-up VAS pain scores for patients who underwent these surgeries. We are hopeful that this data will provide better comparison between the two methods of analgesia once the effects of ISB have worn off.

# Incidence and Risk Factors for Bilateral Patellofemoral Instability

Cole Pennock, Qiang An, Robert Westermann, MD, Kyle Duchman, MD

**Background:** Patellofemoral joint instability is common in young athletes and often requires surgical intervention. Incidence and risk factors for ipsilateral instability recurrence have been more discussed in the literature than contralateral instability events.

**Purpose:** To evaluate the incidence and risk factors for contralateral patellofemoral instability in patients who have undergone patellar stabilization surgery.

**Methods:** This retrospective study included 543 patients who had undergone medial patellofemoral ligament reconstruction and/or Fulkerson osteotomy as surgical management for lateral patellofemoral instability. The medical records of these patients were examined to evaluate the non-surgical knee. Available imaging of each affected knee was examined to evaluate for patella alta, skeletal maturity, trochlear dysplasia, tibial tubercle to trochlear groove (TT-TG) distance, and tibial tubercle to posterior collateral ligament (TT-PCL) distance. Demographic factors such as BMI, age, and sex were also examined. A second study was done excluding patients with previous history of bilateral instability, assessing risk factors using the same methods. This yielded information about incidence and risk factors of "new onset" contralateral instability post-surgery.

**Results:** Of the 543 patients examined, 205 (37.8%) had evidence of contralateral instability in the medical record. Patella alta (OR, 2.4), skeletal immaturity (OR, 2.67), and lower age ($p<0.0001$) were associated with increased risk of bilateral instability in this cohort. Sex, BMI, TT-TG distance, and TT-PCL distance, and trochlear dysplasia were not shown to be associated with increased risk of bilateral instability. In the second study, 63 out of 401 (15.71%) of patients had evidence of new onset contralateral instability post-surgery. Skeletal immaturity (OR, 6.64) was found to be associated with increased risk of instability.

**Conclusion:** Incidence of contralateral (bilateral) patellofemoral instability was found to be 37.8% in the present series. Lower age, skeletal immaturity, and patella alta were found to be associated with increased risk of bilateral instability. Incidence of new onset contralateral instability was found to be 15.71% and was associated with skeletal immaturity.

**ABSTRACT**

**The Ocular Trauma Score Underestimates Visual Recovery for the Most Severe Open Globe Injuries**

Student: Eli A. Perez
Mentor: Jonathan F. Russell

**Purpose:** To compare visual outcomes after open globe injury (OGI) to those predicted by the Ocular Trauma Score (OTS), and to investigate the effect of treatment with pars plana vitrectomy (PPV)

**Design:** Retrospective cohort study of patients presenting with OGI to an academic U.S. ophthalmology department from 2017 to 2020

**Methods:** Best-corrected visual acuity (VA) measurements at last follow-up were compared to final VA predicted by the OTS, based on pre-operative injury characteristics. Last recorded VA of patients treated with PPV during initial OGI repair (Primary PPV group) were compared to patients treated with PPV after initial OGI repair (Secondary PPV group) and patients never treated with PPV (No PPV group).

**Results:** One-hundred thirty-three subjects with OGI were identified and analyzed. The overall rate of PPV was 32%. Predictors of worse VA at last follow-up included older age ($P=0.047$) and worse presenting VA ($P<0.001$). VA outcomes for eyes in OTS Categories 2-5 did not significantly differ from OTS predictions. However, eyes in OTS Category 1 had a higher likelihood of light perception to hand motion VA (46% in the study cohort vs. 15% predicted by the OTS, $P=0.004$) and lower likelihood of no light perception (33% vs 74%, $P<0.001$). The Secondary PPV group had the worst VA at presentation amongst the three groups ($P=0.016$), but VA at last follow-up did not significantly differ between the study groups ($P=0.338$).

**Conclusions:** The most severe OGIs (i.e., OTS Category 1) had better visual outcomes than predicted by the published OTS expectations, and secondary PPV was associated with significant visual improvement despite poor prognostic predictions. Evaluation by a vitreoretinal surgeon should be considered for all patients with severe OGI, especially those in OTS Category 1.

Evaluating Contextual Factors Associated with the Use of an mHealth Intervention by Community Health Workers in Togo, West Africa

Maiti Peters, Elissa Z. Faro, PhD, Jessica Haughton, Desire Dabla, Essodinam Miziou, Dawkin's Kamara, Etonam Sowu, Hyacinthe Awizi, Tsolegnagbo P. Kossi, Kelly Lue, Sébastien Osterrieth, Amanda W. Singer

**Background**
Community Health Workers (CHW) constitute the critical frontline of the healthcare system and their effectiveness is influenced by factors such as training, payment, and sufficient support and supplies. Advances in data science and the increasing functionality of digital technologies have created opportunities to transform community health. Thorough evaluation of these digital tools and their implementation is necessary to document their impact on health.
**Purpose**
Many mHealth clinical decision-making tools have been evaluated from the perspective of the users, but few have assessed patient experience. Our research project used the roll-out of a new clinical decision support app in Togo, West Africa as an opportunity to assess its functionality, feasibility, usability, and acceptability among patients as well as CHWs. The app is a web-based clinical decision support tool that uses physician-developed algorithms to guide frontline providers through assessment, triage, treatment, and follow-up guidelines. The project emphasized understanding the impact of the tool on CHW-patient interactions, especially patient confidence in the care they receive and the likelihood that they will adhere to treatment recommendations. Quantitative data from the app were collected concurrently with the qualitative interviews for triangulation of the data to enhance validity.
**Methods**
We conducted mixed-methods research using qualitative interviews and quantitative administrative data collected from the app. We used the Practical Robust Implementation and Sustainability Model (PRISM) implementation framework to develop the interview guides and to inform data analysis. PRISM emphasizes the importance of contextual factors in the implementation of evidence-based interventions. Quantitative data were collected concurrently with the qualitative interviews. After identifying the five most common conditions for which CHWs used the app for clinical decision support, five patients per condition formed the patient sample. Team members conducted in-person semi-structured interviews with 22 CHWs and 21 patients. The qualitative data were analyzed using rapid qualitative methods and triangulated with the quantitative data from the same period.
**Results**
While the CHW perspective was overwhelmingly positive towards the app, there were some negative perceptions around practicality, data, reporting, and certain clinical aspects, such as discrepancies between local treatment guidelines and recommendations in the app. CHWs reported that patients had a positive view of the app but overall suggested more organizational support, such as ongoing training and infrastructure. Like the CHWs, the patient perspective of the app was generally positive, specifically on the speed of the app, its effectiveness, and the ability to better understand health check-ups. The quantitative user app data confirmed the qualitative findings and provided the implementation team with stratified data to target further support.
**Discussion/Conclusion**
With very few assessments of the patient experience with mHealth interventions, this study found that a mobile-decision support tool led to a greater patient trust in CHWs and improved CHW self-confidence in their treatment recommendations and greater patient trust and rapport-building. While attitude towards the app was positive, major implementation challenges were discovered, including technical problems, discrepancies between the app recommendations and clinical training and data and reporting issues. Our research findings were shared with the Integrate Health program team in real-time to inform iterative improvements in implementation including (1) systematically tracking and resolving discrepancies in recommendations vs local guidelines; (2) streamlining app usage and clinical data collection; (3) developing support tools for real time troubleshooting technical issues; (4) resolving infrastructure issues like solar panels for charging in the field; and (5) sharing feedback data with the CHWs to improve adoption and uptake.

# Postoperative Muscle Relaxant Use Associated with Increased Risk of Delirium Following Lumbar Spinal Fusion

Piscopo A, Perez E, Woodroffe R.

Introduction:
Muscle relaxants including cyclobenzaprine and baclofen are frequently utilized in pain management following spine surgery as part of enhanced recovery after surgery (ERAS) protocols. These medications are associated with anticholinergic and central nervous system side effects and are used with caution in outpatient treatment for those at high-risk of delirium, especially the elderly. Literature investigating their association with delirium in the postoperative setting has not been described.

Objective:
Investigate whether the administration of muscle relaxants affects the incidence of postoperative delirium in elderly patients undergoing lumbar spinal fusion.

Method:
Patients over age 65 undergoing elective posterior lumbar fusion between 2017 and 2021 at the senior author's institution were retrospectively reviewed. Variables collected included patient demographics as well as whether subjects received postoperative administration of baclofen and/or cyclobenzaprine on postoperative day 1 as part of a multimodal analgesia regimen. Doubly-robust inverse probability weighting (IPW) with cox-regression was used to evaluate the incidence of postoperative delirium between groups.

Result:
Five-hundred and thirty-one patients were included in the analysis. Incidence of delirium in those who received postoperative muscle relaxants was 17.6% (44/250) compared to 11.4% (32/281) in the control group who did not (p=0.001). Doubly-robust IPW analysis found patients who received muscle relaxants were at a 2.07 (95% CI: 1.18-3.63) times increased risk of delirium compared to controls (p=0.015). Postoperative time to delirium onset was similar between groups (3.0 vs 3.1 days; p=0.916) while the average duration of delirium was significantly longer in those who received postoperative muscle relaxants (2.5 vs 1.6 days; p=0.008).

Conclusion:
Postoperative muscle relaxant use was associated with a higher risk of delirium in elderly adults following lumbar spinal fusion. Although muscle relaxants may assist with postoperative pain control as part of ERAS protocols while minimizing opioid administration, their side effect profile should be considered in patients at high risk of postoperative delirium.

# Linezolid Resistant *Staphylococcus aureus* in Patients with Cystic Fibrosis

by
Nicholas J. Pitcher, Andries Feder, Nicholas Bolden, Christian F. Zirbes,
Andrew L. Thurman, Valerie L. Reeb, Harry S. Porterfield, Ahmed Moustafa,
Paul Planet, and Anthony J. Fischer

**Background**: Patients with cystic fibrosis frequently receive antibiotics to treat chronic methicillin resistant *Staphylococcus aureus* (MRSA) infections. Linezolid is an effective antibiotic for the treatment of *Staphylococcus aureus* infections. Resistance to linezolid is considered rare in *S. aureus* but could emerge with repeated dosing. We recently reported widespread prescription of linezolid for a cohort of patients with cystic fibrosis (CF).

**Objectives:** The goals of this study were to determine the incidence of linezolid resistance in CF and determine molecular mechanisms of linezolid resistance.

**Methods:** We collected retrospective microbiology reports for patients attending the University of Iowa CF Center between 2008 and 2018. We identified subjects with *S. aureus* resistant to linezolid (MIC > 4). We obtained susceptible and resistant isolates from these patients and retested susceptibility to linezolid using broth microdilution. We then sequenced whole genomes for each isolate on the Illumina platform and determined multilocus sequence type (ST) in Bactopia. We assembled sequences with SPAdes and used HISAT2 to align assemblies against a reference. We identified nucleotide changes between resistant and susceptible isolates using Arraystar.

**Results**: Between 2008 and 2018, 111 patients received linezolid. 4 of these patients cultured linezolid resistant *S. aureus*. These subjects had between 8 and 20 different orders for linezolid. We sequenced 11 linezolid resistant and 21 susceptible isolates from these 4 subjects. Linezolid resistance developed independently based on phylogenetic analysis and was found on sequence type 5 and 105 background. One subject had 4 resistant isolates with multiple mutations in ribosomal subunits and hypermutation due to loss of DNA repair genes mutS and mutL. Another subject had the G2603T 23S rRNA variant previously associated with linezolid resistance. In two subjects, the genetic basis for resistance was unclear. Linezolid resistance did not persist in three subjects, suggesting that this adaptation may decrease overall fitness.

**Conclusions:** Linezolid resistance evolved independently in 4 of 111 patients in this study. We did not find evidence of linezolid resistant *S. aureus* transmission within the CF center. The emergence of linezolid resistance occurred by independent genetic mechanisms. All resistant strains developed on ST5 or ST105 MRSA.

**Medical Student Research Conference - Fall 2022 Abstract Submission**

**Faith Prochaska [faith-prochaska@uiowa.edu]**

# Pharmacological reduction of the innate immune response suppresses seizures in a *Drosophila* model of epilepsy

Faith Prochaska, Anthony Lilienthal, Krishna Nukala, Dr. J. Robert Manak

Previous work in the Manak lab has shown that mutations in *prickle (pk)* cause an epilepsy-ataxia syndrome in *Drosophila*, similar to what is observed in humans with mutations in orthologous *PRICKLE* genes. Drosophila *pk* mutant brains show elevated, sustained neuronal cell death correlating with increasing, progressive seizure penetrance as well as an increase in both the innate immune response (IIR) and oxidative stress. Additionally, using genetic knockdown and overexpression approaches, reduction of the immune response was shown to suppress neuronal cell death which in turn led to suppression of seizures. Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) has been previously shown to increase lifespan and improve motor function in aging or disease models of *Drosophila*. We hypothesized that treating seizure-prone *pk* mutants with NSAIDs would improve neuronal function, reduce IIR and neurodegeneration, and thus suppress seizures. Using a spontaneous seizure assay to quantify unprovoked seizures in *pk* mutants, preliminary data indicates that valeroyl salicylate, but neither licofelone nor trans-resveratrol, can significantly suppress seizures thereby indicating that valeroyl salicylate may be a promising drug to help treat progressive epilepsies. It was additionally shown that *Drosophila* models of more common human epilepsies associated with ion channel mutations also show unprovoked spontaneous seizure activity, thereby establishing new fly models for assessing IIR involvement in epilepsy progression.

**TITLE:** 3D Aneurysm Wall Enhancement is Associated with Symptomatic Presentation

**AUTHORS:** Ashrita Raghuram BSE[1], Sebastian Sanchez MD[1], Linder Wendt MS[4], Steven Cochran BS[5], Daizo Ishii MD[2], Carlos Osorno-Cruz BS[2], Girish Bathla MD[3], Tim Koscik PhD[5], James Torner PhD[2,4], David Hasan MD, MSc[6], Edgar A Samaniego MD,MS [1,2,3]

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## ABSTRACT:

*Introduction/Purpose:* Aneurysm wall enhancement (AWE) is a potential surrogate biomarker for aneurysm instability. Previous studies have assessed AWE using 2D multiplanar methods, most of which were conducted qualitatively. A new quantitative tool to map 3D-AWE of brain aneurysms was studied on a large cohort of patients.

*Materials and Methods:* Saccular aneurysms were imaged prospectively with 3T high resolution magnetic resonance imaging (HR-MRI). AWE patterns of symptomatic and asymptomatic aneurysms were analyzed with our 3D-AWE pipeline. Symptomatic aneurysms were defined as ruptured, presentation with sentinel headache, and presentation with cranial nerve neuropathy. Aneurysms were segmented and orthogonal probes were extended into the aneurysm wall to create 3D-AWE maps. Three metrics were used to characterize enhancement: 3D circumferential AWE (3D-CAWE), aneurysm-specific contrast uptake (SAWE), and focal AWE (FAWE). Aneurysms with a circumferential AWE higher than the corpus callosum (3D-CAWE $\geq$ 1) were classified as 3D-CAWE+. Symptomatic presentation was predicted with univariate and multivariate logistic models. Aneurysm size, size ratio, aspect ratio, irregular morphology, and PHASES and ELAPSS scores were compared with the new AWE metrics. Compartmental bleb analysis and identification of microhemorrhages were also performed.

*Results:* Ninety-three aneurysms were analyzed. Univariate analysis showed that 3D-CAWE, SAWE, and FAWE are predictors of symptomatic status (OR = 1.34, 1.25, and 1.08 respectively). A multivariate model including aneurysm size, 3D-CAWE+, age, female sex, and FAWE predicted symptomatic status with 80% specificity and 90% sensitivity (AUC = 0.914, NPV = 0.967). FAWE was also associated with irregular morphology and high-risk location ($p$ = 0.043, $p$ = 0.001 respectively). In general, blebs enhanced 56% more than the aneurysm body. Areas of microhemorrhage colocalized with increased SAWE ($p$ = 0.047).

*Conclusions:* Analysis of enhancement with 3D-AWE maps provides a new set of metrics that could potentially improve the identification of symptomatic aneurysms.

**Pain Interference and Fatigue in Limb-Girdle Muscular Dystrophy R9, *FKRP* Related**

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*Background*: Limb-girdle muscular dystrophy (LGMD) R9 is an autosomal recessive disorder caused by variants in the fukutin-related protein (*FKRP*) gene. Global registry data indicates a high prevalence of pain in individuals with LGMDR9, likely due to muscle pain and cramps following exertion. However, it is unknown how much this pain interferes with daily living and how it correlates with fatigue.

*Purpose*: To better understand the patient experience, this study quantified the prevalence and severity of pain interference and fatigue in individuals with LGMDR9. Further, we explored their associations with age, sex, and motor function.

*Methods*: Participants enrolled in an ongoing dystroglycanopathy natural history study with documented *FKRP* variants were followed longitudinally. They completed Patient-Reported Outcomes Measurement Information System (PROMIS) pain interference and fatigue short forms at annual visits across the span of seven years. Raw scores were converted to standardized T-scores for comparison with the general U.S. population (mean = 50, standard deviation = 10). General guidelines for T-score cut points were used to group results into Normal, Mild, Moderate or Severe categories. Motor function was annually evaluated with 10-meter walk/run (10MW/R) and 4-stair climb (4SC) assessments. Linear mixed models were used to estimate the severity and correlations of pain interference and fatigue.

*Results:* 23 children (age = 11.7 ± 3.5 years) completed a total of 56 pain interference and fatigue short forms. 54 adults (age = 38.5 ± 13.6 years) completed 170 short forms. Estimated mean pain interference T-scores were 48.5 (45.5 – 51.6) in children and 51.6 (49.5 – 53.6) in adults. 58% of participants had pain interference greater than expected in the general population at least once during the study. 50% of those with two or more visits had variable pain interference that changed across PROMIS cut point categories. Estimated mean fatigue T-scores were 49.0 (45.3 – 52.6) in children and 55.1 (53.0 – 57.2) in adults. 75% experienced increased fatigue compared to the general population, and fatigue was severe in 6%. 68% (≥2 visits) had variable fatigue levels. Pain interference and fatigue were positively correlated, r = 0.55 (0.38 – 0.69). Both increased with older age, and neither differed by sex. Pain interference did not correlate with motor function. However, fatigue negatively correlated with 10MW/R speed, r = -0.32 (-0.53 – -0.03) and 4SC speed, r = -0.35 (-0.57 – 0.03) in adults but not children.

*Conclusions*: Individuals with LGMDR9 had pain interference levels similar to what is expected in the general population. We suggest that the episodic nature of pain in this disease makes it less likely to interfere with daily living. Fatigue was increased in adults and worsened with age and declining motor function. Energy management strategies, such as activity pacing and assistive devices, may be considered as fatigue progresses in individuals with LGMDR9. Our results indicate that fatigue as measured by patient reported measures could be an interesting outcome measure in clinical trials.

**Exploring Spiral Ganglion Neuron Pathfinding and Ability to Turn in Response to Biophysical Cues**

Madeline Rhomberg: Mentored by Marlan Hansen, Collaborating with Allan Guymon

**Background**: Spiral Ganglion Neurons (SGNs) transmit electrical signals that enable the perception of auditory stimuli. The intricate tonotopic organization of SGNs and their respective hair cells in the cochlea enable differentiation of varying sound frequencies. This precise arrangement is achieved by directed neurite growth through a mechanism called pathfinding wherein the growth cone at the neurite's tip acts to sense biochemical and biophysical cues that orient growth toward a target. An understanding of neuron pathfinding has many clinical applications. The interest in SGNs specifically stems from a drive to improve the efficacy of cochlear implants (CIs) at correctly transmitting auditory signals. These devices rely on a high-resolution signal at the neural-electrode interface. An objective of our ongoing research is to better understand the mechanisms of pathfinding to optimize neurite integration into neural prosthetics, such as CIs, by directing neurite growth onto the prosthetic's surface or into its outer coating. We chose to utilize a novel multi-angle channel micropatterned substrate to better understand the limitations and ability of SGNs to turn in response to biophysical cues.

**Aims**: This research informs the basic biological processes enabling SGNs to sense and turn in response to biophysical substrate cues and neurite growth cone behaviors required to direct SGN growth toward targets, such as cochlear implants.

**Methods**: multi-angle channel micropatterned materials were made from a 40% HMA, 59% HDDMA, and 1% photo-initiator solution, covered with a photomask, and exposed to UV light in order to create micropatterns of 2um, 4um, and 8um amplitudes as well as a flat photopolymerized control. SGNs were dissected from neonatal mice, cultured on micropatterned features, and the behavior and ability of SGNs to follow complex angle channels (30°, 45°, 60°, 90°, and 120°) was assessed through immunofluorescent labeling of NF200 and live cell imaging. Measures of turning behavior in fixed samples included length in channel and proportion successfully turning.

**Results**: Data indicated that the length of the neurite in the channel increases with increasing amplitude and more gradual turns. Additionally, the proportion of neurites turning in response to the channel cues increased with amplitude. For live cell imaging, the growth cones remain in the channel at a much greater proportion in the 8um amplitude substrate compared to the 4um substrate. This system also demonstrated that neurite shafts reorient across the turns during neurite guidance.

**Conclusion**: The geometry of the complex channels determines the ability of SGN neurites to follow the angled turns; however, the dynamics of neurite growth and the decisions the growth cone makes to create this alignment remain uncertain. Although, our real time system suggests that the morphology and behavior of neuron growth cones and their interactions with micropattern ridges drives guidance. The novel multi-angle channel micropatterned substrate proved to be an efficient system for assessing the ability of SGNs to turn in response to biophysical cues and can be used to probe the signaling pathways by which neurons sense and navigate these turns.

Title: Prepectoral vs. Subpectoral Plane in Post-Mastectomy Direct-to-Implant Reconstruction

Student: Braden Rolig, M2
Mentor: Dr. Kelly Ledbetter, M.D.
Department: Surgery, Division of Plastic Surgery

## Background

Post-mastectomy breast reconstruction has been shown to improve quality of life, self-esteem, and body image.[1] An increasing proportion of women undergoing therapeutic and prophylactic mastectomy elect to proceed with breast reconstruction: 46% in 1998 and 63% in 2007.[2] There has also been an increase in the proportion of women electing to undergo bilateral mastectomy compared to unilateral mastectomy. Of all mastectomies performed in 1998 only 3% were bilateral. In 2007, bilateral mastectomies constituted 18% of all mastectomies.[2] Over the same period, use of implant-based reconstruction methods increased while use of autologous methods declined.[2] Today, approximately 80% of post-mastectomy reconstruction procedures utilize an implant-based approach.[3] All of these trends demonstrate the increasing demand for efficacious post-mastectomy implant-based reconstruction.

Historically, plastic surgeons predominately utilized the subpectoral approach for implant-based reconstruction. However, the prepectoral approach is now favored over the sub-pectoral approach in many instances. In the prepectoral approach the pectoralis major muscle remains in its anatomic position and the implant, commonly wrapped in an acellular dermal matrix, is placed anterior to the pectoralis major muscle. The prepectoral plane offers many advantages including decreased rates of animation deformity, decreased operative time, lower reported post-operative pain, and lower rates of capsular contracture.[4] However, there are still many contraindications to prepectoral implant-based reconstruction including, but not limited to, thin mastectomy flaps, lack of fat donor sites, active smoking, and history of prior radiation therapy.[5] Understanding the relative risks in the context of a patient's oncologic and demographic characteristics will help surgeons determine the safest and most efficacious approach for implant-based reconstruction.

## Methods

A retrospective chart review was completed for a comprehensive breast reconstruction database. 1,047 patients who underwent breast reconstruction-related procedures at UIHC were identified within the specified time frame (1/1/2012-12/31/2021). To date, 600 cases have been analyzed. Of these 600 cases, 462 met inclusion criteria for the database. 204 (44.2%) patients underwent direct-to-implant (DTI) reconstruction. Of the patients who had DTI reconstruction, 79 patients (38.7%) underwent prepectoral reconstruction and 125 patients (61.3%) underwent subpectoral reconstruction. In total, 135 breasts were reconstructed with a prepectoral implant, and 180 breasts were reconstructed with a subpectoral implant. The primary outcomes of this study included incidence of returning to the operating room for an acute complication and total number of additional surgeries following reconstruction. Secondary outcomes include rates of post-operative acute complications (hematoma, seroma, cellulitis, abscess, and dehiscence) and long-term complications (implant rupture, capsular contracture, rippling, malposition, asymmetry, and infection).

## Results

Those who underwent prepectoral and subpectoral DTI reconstruction returned to the operating room due to acute complications at the same rate (18.99% and 18.4%, respectively). Additionally, the groups did not differ in the percentage of women who underwent at least one additional procedure acutely or long-term (60.76% prepectoral and 56% subpectoral). The average number of additional surgeries in the prepectoral and subpectoral groups was 1.16 and 1.23, respectively.

## Discussion

Of note, the two groups differed significantly in time elapsed since undergoing reconstruction. The average amount of time since surgery was 2.77 years for the prepectoral group and 5.73 years for the subpectoral group (p-value <.0001). This limits our ability to accurately compare the two groups in the long-term, however, this difference was expected due to the relatively recent paradigm shift in plane used for implant reconstruction. Continuing to follow these cohorts will allow us to further analyze the long-term complications of these two reconstruction techniques.

## Predictors and Impact of Pneumonia on Adverse Outcomes in Inhalation Injury Patients

Nicolas Ronkar, BS; Colette Galet, PhD; Lucy Wibbenmeyer, MD

**Background.** Next to age and burn size, the presence of inhalation injury (II) is the third mortality prognostic factor for burn injury. II is the result of heat or toxic chemicals of combustion that injure the respiratory epithelium, essentially producing a burn to the airway. This injury can lead to an inflammatory state setting off a cascade that leads to denaturation of protein, cellular death, and profound edema. Fiberoptic bronchoscopy (FB) remains the gold standard for diagnosing II with scoring related to the amount and location of soot, edema, and ulceration (none, mild, moderate, and severe).Treatment for II is generally supportive with a goal to prevent additional lung injury or complications. Treatments include intubation, appropriate resuscitation of the cutaneous burn, protective ventilation strategies, repeated FB, and chemical lysis of airways casts. Still, with the most attentive care, II can lead to pulmonary complications such as pneumonia, acute respiratory distress syndrome (ARDS), and acute lung injury (ALI), all of which have been hypothesized to increase mortality in II. The goal of this study was to 1) Identify variables associated with the risk of developing pneumonia; 2) Determine the impact of pneumonia on selected outcomes, specifically ventilator days, hospital length of stay (LOS), the development of ARDS, and death.

**Methods.** De-identified data from the ABA sponsored Prospective Inhalation study (ISIS) were used. II was confirmed by FB. Baseline demographics, injury data, burn size, laboratory data, treatment, and hospital course were recorded. Ventilator use, complications, including pneumonia, ARDS, and death, were tracked daily for seven days and then weekly until discharge. Univariate and multivariate analysis were performed using SPSS 28.0. Variables included in multivariate analysis had a p value of 0.1 or less. $P < 0.05$ was considered significant.

**Results.** A total of 108 subjects were enrolled in the ISIS study, 106 had complete data and were included in the analysis. Median age was 48.5 y, 59.4% of the subjects were male, 76.4 White and 9.4 Black. In terms of complications, 46.2% of the subjects developed pneumonia, 11.3% ARDS, 9.4% Acute Lung Injury (ALI), and 17% died. On univariate analysis, subjects who developed pneumonia were more likely to be white (87.8% vs. 66.7%, $p = 0.006$), to present with higher total burn surface area (24.70 [8.00 - 49.50] vs. 2.85 [0.00 - 25.38], $p = 0.002$) and full thickness burn (55.1% vs. 31.6%, $p = 0.018$), and to require tracheostomy during admission (57.1% vs. 12.3%, $p < 0.001$). Pneumonia cases stayed significantly longer in the hospital (24 [15-77.5] vs. 6 [3-20], $p < 0.001$) and on the ventilator (17 [9-33] vs. 2 [1-5.5], $p < 0.001$). They were also more likely to receive colloids during the first 24h of admission (29.2% vs. 22.8%, $p <0.001$) and to develop other respiratory complications, including ARDS, ALI, and respiratory failure; mortality rate was similar to that of subjects who did not develop pneumonia. Plasma levels of MMP-9 tended to be lower than that of subjects who did not develop pneumonia (183.93 [107.08 - 302.09] vs. 242.77 [141.78 - 680.22], $p = 0.056$). All pneumonia subjects received antibiotics either before or at the time of pneumonia diagnosis. On multivariate analysis, being white ($p = 0.033$), and receiving colloids in the first 24 h of admission (OR= 3.582 [1.157-11.087], $p = 0.027$) were associated with increased risk of pneumonia. 2nd degree burn (OR = 1.052 [0.997-1.109], $p = 0.065$) showed a trend but was not significant. Higher level of MMP-9 in the plasma (OR= 0.999 [0.998-1], $p = 0.041$) lowered the risk of pneumonia.
Looking at the impact of pneumonia on other outcomes, on multivariate analysis, pneumonia was not associated with higher risk of developing ALI or mortality but was associated with increased risk of developing ARDS (OR = 8.496 [1.322-54.61], $p = 0.024$). Controlling for age, gender, race, TBSA, 2nd and 3rd degree burn, developing pneumonia was associated with longer hospital length of stay (B = 15.2 [2.4-28], $p = 0.020$) and higher number of days on a ventilator (B = 15.6 [8.2-23], $p < 0.001$).

**Conclusion**. Pneumonia remains a high-risk complication affecting nearly half of the patients in the current study which comprises the largest prospective inhalation cohort to date. Pneumonia is associated with increased LOS and ventilator days. On multivariate analysis, those who received colloids were 3.5 times more likely to develop pneumonia. Although only weakly associated, MMP-9 may be a marker of those who are inclined to develop pneumonia. Future studies are warranted to analyze the relationship between pneumonia and inhalation injury severity and various inflammatory bronchoalveolar lavage (BAL) and serum markers to establish levels indicative of disease.

Title:Niemann-Pick Disease Type C Resulting from Uniparental Isodisomy of Chromosome 18
Student: Allyson Rose
Mentor: John Bernat MD, PhD

Niemann-Pick Disease Type C is an autosomal recessive neurodegenerative disorder with an incidence of 1 in 100,000-150,000 that is characterized by the over-accumulation of cholesterol and glycosphingolipids. The buildup of these materials in the liver, spleen, brain or lungs may lead to symptoms such as hepatosplenomegaly, jaundice, hypotonia, developmental delay, ataxia, or seizures. Ninety-five percent of Niemann-Pick Disease Type C cases result from a mutation in the *NPC1* gene, which encodes for a membrane glycoprotein on chromosome 18. Here, we present the case of a young woman diagnosed with Niemann-Pick Type C resulting from a suspected uniparental isodisomy of chromosome 18. The patient presented with mild intellectual disability, a history of difficulty swallowing, seizures, and Hashimoto's thyroiditis. Testing showed a large region of single nucleotide polymorphism homozygosity (chr18:18516680-45815417) [hg19] that includes the *NPC1* gene. Elevated plasma oxysterols and sequencing of the *NPC1* gene demonstrated a homozygous pathogenic variant (c. 3019C>G, p.Pro1007Ala) that further confirmed the Niemann-Pick Type C diagnosis.

**Title**
Efficacy of Ultrasound-Guided Percutaneous Tenotomy and Platelet-Rich Plasma Injections for Lateral Epicondylitis

**Authors**
Marshall Rupe, Ignacio Garcia Fleury, Ryan Kruse, Joseph Buckwalter V.

**Background**
Lateral epicondylitis (LE) has an estimated incidence of 3.3-3.5 per 1000, or 1 million cases per year in the United States [1]. Even though LE is common, there is still debate on the best treatment strategy [2]. Surgical treatment has been a viable option for decades, but recently newer, minimally invasive options have emerged that can allow patients to have a quicker recovery while also avoiding the more invasive surgical treatments. Two of these minimally invasive approaches are platelet-rich plasma (PRP) injections and ultrasound-guided percutaneous tenotomy (USGPT). These two procedures have been shown to be effective with significant improvement in pain and function scores [3]. However, given the novelty of these treatments, there has been little to no investigation of risk factors associated with failure for PRP or USGPT.

**Purpose**
The purpose of this study is to establish risk factors for failure of both PRP injections and USGPT and to assess the efficacy of both procedures.

**Methods**
This study was a retrospective review that included patients with LE treated by PRP injections or USGPT. Subject characteristics including demographics, comorbidities, and injury history were obtained through medical charts. The primary outcome was surgical indication within a year post-procedure, which was classified as a failure. Subject characteristics were analyzed as risk factors for failure. Additionally, Patient Reported Outcome (PRO) measures were recorded prior to the procedure and at 3 follow-up appointments at 2, 6, and 12 weeks. PROs used were Ortho Pain 4 and Patient Reported Percent Improvement as per the standard of care at our institution. The secondary outcome was pain improvement using these PROs.

**Results**
96 procedures were included in the study, 39 PRP and 57 USGPT. 33/39 (84.6%) PRP injections were successful and 50/57 (87.7%) of USGPT procedures were successful. Of the variables assessed, common extensor tendon tearing and worker's compensation cases were associated with failure in the USGPT group with Odds Ratio (OR) of 7.71 ($p = 0.0233$) and 31.50 ($p = 0.0026$) respectively. In the PRP group, lateral collateral ligament complex (LCL) involvement and LCL injection were associated with failure with OR of 11.80 ($p = 0.0112$) and 35.00 ($p = 0.0035$) respectively. Additionally, there were statistically significant decreases in pain in all 4 questions of Ortho Pain 4 and in the reported percent improvement for both PRP and USGPT groups through the 12-week follow-up.

**Discussion**
Common extensor tendon tearing and worker's compensation cases were risk factors for failure of USGPT for LE. Risk factors for PRP injections were LCL involvement and injection. The LCL is typically only injected when there is overt involvement, so LCL injection as a risk factor is likely a reflection of LCL involvement being a true risk factor. Both procedures were found to be efficacious, with success rates of roughly 85% and statistically significant improvement in the 2 PROs used in the study. These risk factors and success rates may be used in patient counseling and patient-physician decision-making regarding treatment options for LE. Future directions could include a prospective risk stratification for the two procedures.

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**Experience with subcutaneous desmopressin in patients with von Willebrand disease (VWD) and qualitative platelet function disorders**

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**Background**: The recent recall of intranasal desmopressin has impacted management of patients with von Willebrand disease (VWD ), leaving one available alternative for home administration: subcutaneous desmopressin preparation at 6 mcg/1.5 ml . With weight-based dosing at 0.3 mcg/kg/dose, individuals >20Kg require multiple injections which decreases convenience and acceptance. We adopted the practice of restricting dosing to two subcutaneous injections (max dose=12mcg) regardless of patient weight. Since the data to support this practice is sparce, we reviewed the response of desmopressin challenge tests for individuals who had both subcutaneous and intranasal desmopressin. The primary objective was to evaluate the hemostatic efficacy of subcutaneous desmopressin based on coagulation parameters during desmopressin challenge tests. The secondary objective was to compare the intra-patient variability between intranasal and subcutaneous challenge tests for patients who underwent testing via both routes.

**Methods**: This retrospective cohort study reviewed seven patients with VWD (type I, II) or associated diseases (low VWF, qualitative platelet disorders) who underwent desmopressin challenge tests via intranasal and subcutaneous routes. An additional seven patients who underwent subcutaneous testing only were reviewed. Response variables included Von Willebrand Factor Antigen (VWF:Ag), VWF:Ristocetin activity (VWF:RCo), and factor VIII levels at baseline and 1 to 6 hours post administration. Response was defined as peak rise in VWF:RCo and FVIII being ≥1.5X baseline and ≥50 IU/dL 1-hour post-administration. Sustained response was defined as VWF:RCo activity ≥50 IU/dL at 4-6 hours.

**Results**: Cohort was grouped into: 1) those who underwent intranasal and subcutaneous desmopressin challenges (n=7) and 2) those who received only subcutaneous (n=7). All patients responded to subcutaneous desmopressin, including three patients in Group 1 who had not originally responded to intranasal administration. There was no significant difference in the mean VWF:RCo peak to baseline ratio between intranasal and subcutaneous routes of administration in Group 1, p=0.107. Of the total 14 patients who underwent subcutaneous desmopressin challenges, 11 were >40kg and received the "limited-dose." These 11 patients met both response and sustained response criteria. The lowest dose used was 0.12mcg/kg in a patient weighing 101.4kg who experienced >2-fold increase in VWF:RCo.

**Conclusion**: Subcutaneous desmopressin should be considered as an alternative to intranasal formulation for home therapy regimen in prevention and treatment of bleeding diathesis in patients with VWD. It is effective at the lower concentration available in the U.S. Additionally, subcutaneous desmopressin testing should be considered for patients unresponsive to intranasal desmopressin.

# A Peripheral Compressive Neuropathy Model to Visualize Pathology at the Neuromuscular Junction

Peter Sanchez, BA, Ignacio Garcia-Fleury, MD, John Davison, MPH, Matt McIlrath, BS, Mitchell Coleman, PhD, Joseph Buckwalter V, MD PhD

**Background:**

Peripheral compressive neuropathies (PCNs) are a frequent cause of disability. The most common PCN is carpal tunnel syndrome (CTS), which results from median nerve compression in the carpal tunnel by the surrounding structures, leading to wasting of the muscle groups distal to the compression. Decompression surgery is frequently a successful treatment option, but the indication for surgical release is less clear in diabetic patients due to difficulty distinguishing PCN from generalized diabetic peripheral neuropathy. To guide the treatment of diabetic PCN, we must further understand the pathophysiology of the disease.

It is well known that nerve transection results in degeneration of the pre-synaptic terminals and upregulation of post-synaptic nicotinic acetylcholine receptors (NAChR). However, the effects of PCNs on the NMJ still remain unclear. Synaptophysin is a presynaptic vesicle protein and NAChR is a motor endplate protein, both of which can be targeted to visualize the NMJ. The purpose of this study is to define if pathological changes occur distal to the site of compression at the neuromuscular junction (NMJ).

**Hypothesis:**

Compression of the sciatic nerve in female Sprague Dawley rats will result in decreased synaptophysin expression and increased NAChR expression. Decompression of the sciatic nerve will result in the opposite effects of compression, until the expression patterns return to baseline.

**Methods:**

Two groups of seven 63-week-old female Sprague Dawley rats were established, a compression group, and a decompression group. In the compression group, animals were sacrificed at 1, 2, 4, 6, 8, 10, and 12 weeks after sciatic nerve compression. In the decompression group, an initial period of 6 weeks of compression was completed in each animal before a decompression procedure. Following decompression, animals were sacrificed at 1, 2, 4, 6, 8, 10, and 12 weeks. The operation was performed on the left hindlimb.

Gastrocnemius/soleus muscle complexes were harvested from left and right hindlimbs, sectioned, and stained with synaptophysin or NAChR antibody. Slides were visualized using brightfield microscopy. Three equally sized images were captured from each slide in a systematic fashion for counting of NMJs. A grid was placed over each image to aid counting. A protocol to count areas of NAChR and synaptophysin stain was established and followed by two independent researchers and PS. Results were recorded in identical excel spreadsheets.

**Results:**

After compression, synaptophysin expression decreased at 2 weeks then increased to above baseline at 12 weeks, while NAChR staining increased at 4 weeks but then returned to baseline. After decompression, synaptophysin decreased over 12 weeks, while NAChR increased at 2 weeks then returned to baseline. Muscle weight decreased by 39.5% after compression and increased after by 71.9% after decompression.

**Discussion:**

Surgical insult, whether compressive or decompressive, results in changes in counted areas of synaptophysin and NAChR staining. Additionally, muscle wasting and regeneration occurs distal to the site of compression. Contrasts in synaptophysin expression may reveal important features of nerve healing responses in compressed and decompressed settings.

**The Effect of Full-Body Weight Loading on Ulnar Variance: An Upper Extremity WBCT Study**

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**Mentor:** Joseph A. Buckwalter V., MD, PhD
**Other Collaborators:** Ignacio Garcia Fleury, MD, Kevin Dibbern, PhD, Jessica Goetz, PhD, Nicole Watson, PhD, Natalie Glass, PhD, Grayson Talaski

**Introduction:** Ulnar variance (UV) is of clinical interest due to its associations with several pathologic wrist conditions, such as triangular fibrocartilage complex tears and ulnar impaction. UV is a measurement that relates the distal articular surfaces of the radius and ulna. A distal projecting ulnar articular surface is defined as positive UV and a distal projecting radial articular surface is defined as negative UV. Neutral UV defines equal projecting articular surfaces. Positive UV is most notably demonstrated in gymnasts, where compounding degeneration can warrant surgical operation and termination from participation in sport. While UV is thought to be dynamic in nature with axial wrist loading, current imaging techniques are restricted to non-weight-bearing modalities that may not accurately depict wrist biomechanics and structure when performing everyday activities. There is a need for a dynamic imaging tool to diagnose symptomatic ulnar positivity under load that may be missed in conventional radiography.

**Purpose:** To investigate how full-body weight loading impacts ulnar variance and to better understand the dynamic, skeletal biomechanics of the wrist.

**Methods:** Subjects completed a forty-five-second scan in a handstand position inside the WBCT on a flat (handstand) and a handlebar (parallettes) platform. Custom attachments were built to support standing on the hands in a CurveBeam HiRise Weight Bearing Computed Tomography (WBCT) machine. A non-weight-bearing CT scan was collected to compare the change in UV upon wrist loading. Subjects performed a handstand on an emed® pressure mapping platform to collect peak force applied to the hands. UV, Radial Inclination (RI), Radial Height (RH), and Volar-Dorsal Tilt (VDT) measurements were completed using Disior Bonelogic™ Hand and Wrist software. Height, age, sex, hand dominance, wrist pain, and prior wrist injury were recorded for fourteen subjects. Those with excessive handstand motion artifacts and injuries that affect biomechanical behavior of the hand were excluded. The relationships between measurements and weight-bearing conditions, as well as subject factors, were analyzed with repeated measures generalized linear regression.

**Results:** Two subjects were excluded from the analysis. The remaining subjects averaged -0.37±1.63mm (left) and -0.15±1.79mm (right) UV on neutral, non-weight-bearing CT. There was a significant, positive increase in average UV from neutral (N) to handstand (H) to parallettes (P) (N-H-P) (0.44±0.21, P=0.0390). RI significantly increased with average UV from N-H-P (0.18±0.07, P=0.0095). Age, sex, height, peak force, hand dominance, prior injury, wrist pain, RH, and VDT were not associated with a change in UV from N-H-P (all $p>0.05$).

**Conclusions/Discussion:** Ulnar variance became more positive when full-body weight was applied to the wrists. The pronated, gripping handstand on parallettes had the most positive UV values on average and is predicted to be the most functional loading mechanism of the wrist. UV was further positively associated with Radial Inclination, suggesting a relationship between UV and force distribution through the radius. Thus, WBCT may be a better tool to measure UV in the gymnast population, with the ability to measure it under functional conditions. Future studies should look to determine UV change in semi-loading conditions to evaluate broader clinical applications of upper extremity WBCT.

# THE EFFECTIVENESS OF A FEMALE PELVIC MEDICINE AND RECONSTRUCTIVE SURGERY DIDACTIC SESSION AND CADAVERIC SIMULATION ON UROLOGY RESIDENTS' KNOWLEDGE OF FEMALE PELVIC SURGERY

Mala Sharma, BS; Annah Vollstedt, MD; Elizabeth Takacs, MD

**Background/Purpose:** Knowledge and application of surgical anatomy is a crucial component of urology residency. However, between the years 2000-2017, performance on the 'Congenital Anomalies, Embryology, Anatomy' category remained consistently low regardless of year in urology residency training. Cadaveric dissection is not commonly used in residency training. A systematic review found that between the years of 2000-2009, only 31% of cadaveric simulations were used for surgical training. The objective of this study was to determine the effectiveness of a didactic and cadaveric simulation training in increasing urology residents' knowledge of female pelvic surgery.

**Methods:** A knowledge-based pretest was administered to trainees at one ACGME-accredited urology residency. The residents participated in a 30-minute didactic session led by a female pelvic medicine and reconstructive surgeon (FPMRS). Residents worked with three FPMRS in the cadaver lab, learning mid-urethral and fascial slings, sacrospinous ligament fixation, and sacrocolpopexy. Upon completion of laboratory session, a knowledge-based posttest and an evaluation of training session was administered. Paired t-tests were used to compare mean pre and posttest scores.

**Results:** Completed pre and posttest knowledge assessments were available for eight residents. There was an increase in number of total correct answers from the pretest to the posttest (5.6 to 15.4 out of 24, $p<0.001$). The average number of correct answers pertaining to anatomical and procedural questions increased from 3.3 to 11 ($p=<0.001$) and 1.5 to 3.9 ($p=0.005$), respectively. The average number of correct answers to functional questions did not improve in the posttest. Six residents completed the training session evaluation. All residents self-reported an increase in knowledge following the training session for all categories (general female pelvic anatomy, retropubic and transobturator sling, sacrocolpopexy, and sacrospinous ligament fixation). All residents agreed that the skills session added value to their education. Five out of six residents answered "extremely satisfied" with the training session and "extremely likely" to recommend a cadaver lab be included in future years.

**Conclusions:** Knowledge and application of surgical anatomy is a crucial component of urology residency. However, the AUA does not require a cadaver lab as a part of the residency curriculum. Moreover, the Anatomy section of the in-service examination is one of the lowest performing categories. The combination of a dedicated didactic session and a cadaveric lab is an effective model for improving urology residents' anatomic and procedural knowledge of FPMRS urology. This model increases residents' anatomic and procedural knowledge. Residents show an objective increase in knowledge and self-reported confidence in the procedures. Overall, the paired didactic and cadaveric session was well received by residents.

# Investigating the Presence of Ferritinophagy in Fuchs Endothelial Corneal Dystrophy

Zachary Shepard; Dr. Mark Greiner, MD; Jess Skeie, PhD; Tim Eggleston; Hanna Shevalye

Background and Purpose: Fuchs endothelial corneal dystrophy (FECD) is a progressive disease that results in the premature death of corneal endothelial (CE) cells. While FECD is the most common disorder of the corneal endothelium and is characterized by accumulations in reactive oxygen species (ROS), relatively little is known about the mechanisms contributing to disease progression. Based on preliminary data demonstrating that iron-dependent lipid peroxidation mediates cell death in FECD, we hypothesized that FECD progression is mediated by alterations in ferritinophagy, a selective form of autophagy that contributes to ferritin degradation and triggers labile iron overload, ROS accumulation, lipid peroxidation, and cell death. The presence of ferritinophagy can be tracked through RNA and protein quantification of several cellular markers, including NCOA4, LC3, and ferritin. We also hypothesized that ultraviolet-A (UV-A) light exposure, which has been demonstrated to contribute to FECD progression and ferroptosis, participates in altered ferritinophagy in FECD.

Methods: We utilized control and FECD cells from cultured immortal cell lines at the Iowa Lions Eye Bank. Cells were treated with various doses of UV-A and antimycin A (AMA) to induce oxidative damage. Protein and RNA markers of ferritinophagy were extracted and analyzed using PCR and microfluidics western blot to confirm the presence or absence of NCOA4. Additionally, treated cells were plated on coverslips, stained via immunohistochemistry, and analyzed using confocal microscopy to further determine cellular changes that may be associated with ferritinophagy in FECD.

Results: Immortalized cell lines affected with FECD demonstrated increased protein levels of the ferritinophagy marker NCOA4 when compared to control cells, indicating that iron accumulation contributed to the cell death characteristic of FECD. UV-A exposure further increased the protein levels of NCOA4 present in FECD cell cultures, demonstrating the effect of UV-A on ferritinophagy in FECD.

Conclusions: Our results reinforce the role of ferritinophagy in FECD by demonstrating an increase of ferritinophagy marker NCOA4 in FECD cell lines. Additionally, this study provides a mechanism for the contribution of UV exposure to disease development, furthering the current understanding of how FECD contributes to cell death and vision loss.

**Preventing preservation-associated oxidative damage in donor corneal endothelial cells**

Student: Bryce Shonka
PI: Mark Greiner, MD
Collaborators: Jessica Skeie, PhD, Hanna Shevalye, and Tim Eggleston

## Abstract

*Introduction*: Cornel endothelial cells (CECs) are post-mitotic and, therefore, have limited ability to regenerate. With age, CEC death causes the nearby remaining cells to enlarge and cover the gaps in the corneal endothelium.[1] Loss of these cells can result in vision loss through corneal edema and haze,[2] as CECs regulate corneal hydration through barrier and pump functions, whereby the passive leakage of fluid through intercellular tight junctions is counterbalanced by Na+/K+-ATPase-mediated pump function.[2] This process requires intact bioenergetic production and substrate utilization.[3] In the setting of donor corneas for transplant, derangement of this process is associated with graft failure that necessitates repeat transplantation. Various research has implicated oxidative stress and mitochondrial dysfunction in the loss of corneal endothelial cells during hypothermic storage of donor corneal tissue prior to corneal transplantation. [4-7]

Manganese superoxide dismutase (MnSOD) is a mitochondrial enzyme encoded by the nuclear *SOD2* gene,[8] and is a key antioxidant enzyme that reduces superoxide radicals ($O_2^{\bullet-}$) generated by mitochondria to hydrogen peroxide ($H_2O_2$),[9, 10] thereby preventing the accumulation of reactive oxygen species (ROS). Recently, MnSOD has been shown to be an important antioxidant enzyme for CEC function. Last year, our group developed an *SOD2* knockout corneal endothelial cell-line and demonstrated bioenergetic changes in mitochondria and increased oxidative damage in CECs that lacked *SOD2*. Since mitochondrial dysfunction and oxidative damage have been implicated in damage to donor cornea tissue, and we recently identified *SOD2* as an important antioxidant in corneal endothelial cells, we sought to evaluate whether an SOD2 mimetic (GC4419) could be used as a treatment to reduce oxidative damage and corneal endothelial cell death in donor cornea tissue.

*Methods:* To quantify SOD2 mRNA expression over time, 16 donor corneas were split into thirds and stored in Optisol-GS storage medium at 4°C for 6, 9, and 13 days. Descemet membrane-endothelial cell complexes were collected from each tissue and RNA was isolated for qPCR with specific SOD2 primers. DMEK-prepared tissue was then taken from a separate set of paired corneas which were split into a GC4419 treatment group and a control group either incubated GC4419-supplemented Optisol-GS storage medium or Optisol-GS alone at 4°C for 5 days. On the day of our assays, multiple 3 mm punches were created per cornea. Mitochondrial bioenergetics were then assayed using Seahorse XF96 extracellular flux analysis. $O_2$ consumption was measured and used to calculate ATP-associated oxygen consumption, proton leak, maximal respiration, spare respiratory capacity, and nonmitochondrial respiration. Oxidative damage was assessed via DHE staining and measurement of DHE and ethidium fluorescence over time. Cell death was then calculated based on nuclear staining with sytox green followed by cell counts. All data were normalized to cell count and analyzed using un-paired t-test.

*Results*: Quantification of SOD2 mRNA via qPCR shows an 8% increase in relative SOD2 mRNA expression at 9 and 13 days of corneal storage, however, this increase is not significant. As such, SOD2 mRNA expression can be considered stable throughout two weeks in storage media. Analysis of mitochondrial bioenergetics indicated no statistically significant difference between GC4419-treated corneal tissue and control in regard to oxygen consumption. Increased non-mitochondrial respiration in GC4419-treated vs control tissue approached significance with a p-value of 0.0570. In assessing oxidative damage and cell death, we found no significant difference between GC4419-treated corneal tissue and control in regard to superoxide formation or cell death.

*Conclusions*: Our preliminary data on SOD2 mRNA expression over time in storage media suggests that levels are stable during the two-week storage period. Additionally, in regard to mitochondrial bioenergetics, superoxide production, and cell death, we found no statistical significance between GC4419-treatment and control at this point, indicating that GC4419 is not harmful to the mitochondrial function of donor cornea tissue and does not increase ROS formation or cell death. It is important to note that these data have limited power due to small sample size, however, moving forward, we plan to continue this study as more tissue becomes available to us. With increased power, we anticipate to see improved mitochondrial function, decreased ROS formation, and decreased cell death in GC4419-treated tissue.

**Examining the Relationship Between Patellar Tendon Thickness and Tendinopathy with ACL Graft Success Rates**

Student: Chirayu Shukla
Mentors: Robert Westermann, MD, and Kyle Duchman, MD

Graft failure after ACL reconstruction surgery can be a severely detrimental outcome. Failure of ACL reconstruction surgeries results in pain and persistent instability, often requiring revision surgery to allow a return to normal daily and athletic activity. As a result, it is essential that potential risk factors for graft failure after ACL are recognized and appropriately addressed when possible. While some factors like younger age, higher activity levels, use of allografts, meniscal deficiency, and cutting sports have shown a positive correlation with graft failure rates, the relationship between the thickness of the patellar tendon and patellar tendinopathy to graft failure rates haven't been studied as much. If a direct relationship between patellar tendon thickness and graft failure rates is established, it could be an important yet easily identifiable risk factor that could be used to determine individuals who may benefit from other autografts such as quadriceps tendon or hamstring tendon reconstruction. This could significantly improve the quality of life for many patients as well as have the potential to save costs for the patient.

We hypothesized that decreased patellar tendon thickness on the sagittal view and the presence of patellar tendinopathy would both be associated with increased graft failure rates following autograft patellar tendon bone-tendon-bone ACL reconstruction surgery.

Using a prospectively collected registry of patients, a retrospective analysis examining patellar tendon thickness was used to determine tendinopathy through MRI analysis using the standards that had been previously established and graded as none, mild, moderate, or severe tendinopathy. 147 patients who had undergone BPTB surgery had their MRIs obtained from the registry, evaluated for tendinopathy, and used to measure the average patellar tendon thickness. Once each patient was graded and measured, whether their graft failed and if they returned to normal activity was also determined. Afterward, the data was analyzed using Fischer's exact test and Wilcox rank sum test to determine significance.

Out of 147 patients, only 6 had their grafts fail. The data showed the average thickness for graft failures was 4.36 whereas non-graft failures had an average thickness of 4.77 ($p = 0.18$); however, the data wasn't significantly different. The data also showed no significant difference in the rates of failure for tendinopathy versus no tendinopathy. While the data seemed to be trending in the right direction with the limited number of failures present, there wasn't enough data to deem the differences statistically significant. In the future more data will need to be collected to solidify the trend and hopefully determine if patellar tendon thickness and tendinopathy are significant risk factors for BPTB ACL surgery.

**Behavioral Characterization of Mouse Models of Scn2a-related Autism**

Student: Jonathan Sikora, M2
Mentor: Aislinn Williams, MD, PhD

**Background:** Autism spectrum disorder (ASD) is estimated to occur in one out of every 54 children, but our understanding of the mechanisms underlying ASD remains limited due to the disorder's remarkably complex etiology. A small percentage of ASD cases are monogenic in origin and can be traced to a single causal mutation, providing an invaluable, simplified model of ASD for correlating molecular dysfunction to phenotype. One such monogenic form of autism, known as Scn2a syndrome, is caused by premature termination codons (PTCs) in the Scn2a gene, which lead to premature truncation of the encoded protein, the sodium channel NaV1.2. Patients with Scn2a Syndrome display a form of syndromic autism that is similar to idiopathic autism, with phenotypes including reduced social interaction and repetitive behaviors. Some patients also have cerebellar signs such as ataxia and cerebellar atrophy highlighting the important role of Scn2a in the cerebellar cortex as well as the cerebral cortex and other brain regions.
Scn2a-associated autism therefore presents an invaluable opportunity to directly investigate the link between a clearly defined etiology (Scn2a haploinsufficiency) and phenotype (Scn2a autism), thereby clarifying at least one possible trajectory that leads to autism. We have developed an Scn2a PTC mouse model with the p.R1626X mutation, a mutation that has been found in humans with Scn2a syndrome. This is the first SCN2A PTC autism rodent model to date. The Scn2a PTC mouse line will provide an opportunity to investigate the effects of Scn2a haploinsufficiency on behavior and neural networking.
**Hypothesis:** We predict that Scn2a p.R1626X mice will have behavioral abnormalities consistent with autism phenotypes, such as deficits in cognitive function and social behaviors, as well as motor and gait adaptation issues.
**Methods:** We recorded USVs for 5 minutes from 9 WT and 15 p.R1626X mice. These recordings were automatically processed and segmented using LMT USV Toolbox to identify every USV in each recording, as well as a number of different relevant parameters (USV duration, maximum frequency, mean frequency, etc.). A separate cohort of 9 WT and 15 p.R1626X mice were used for a battery of 7 different tests in order to assess motor function, gait, associative learning, gait adaptation, activity levels, anxiety levels, sociability, and exploratory behavior.
**Results:** We found no significant differences between our WT and p.R1626X mice when comparing USV count, USV duration, maximum USV frequency, mean USV frequency, minimum USV frequency, motor function, gait, associative learning, exploratory behavior, or sociability. However, we did find that our p.R1626X mice displayed impaired gait adaptation ($p = 0.0427$) and an anxiolytic phenotype ($p = 0.0141$) compared to our WT mice.
**Discussion:** The observed differences in gait adaptation were largely driven by our WT females ($n = 4$), meaning this analysis may benefit from future studies with larger sample sizes. The anxiolytic phenotype observed in our p.R1626X mice is the opposite of what we hypothesized, however this finding is consistent with other Scn2a mouse models. Perhaps this could point towards involvement of the Scn2a gene in the development of neural circuits associated with avoiding danger. Overall, these findings suggest that our mouse model has some phenotypic features consistent with human Scn2a-related autism, although it does not recapitulate all features of the syndrome.

**Title:** Understanding Food Insecurity in Pregnancy Outside the Clinic Encounter
**Student**: Megan Sinik
**Mentor**: Dr. Michael Haugsdal, Department of Obstetrics and Gynecology
**Other Collaborators:** Dr. Craig Syrop, Reproductive Endocrinologist; Betty Tu, Carver College of Medicine

**Background and Rationale:** Pregnancy represents a critical life course event where proper nutrition is crucial for the long-term health of both the mother and fetus. Pregnant women, particularly pregnant women of color and pregnant women with children are at risk for food insecurity. In 2017, a social determinant needs assessment among our obstetrics patients demonstrated that up to 40% were experiencing the negative effects of social determinants of health, primarily food insecurity (FI), In response, the Upstream Initiative was created as a student run, faculty mentored program where student volunteers screen all patients within the High-Risk Obstetrics (HROB) Clinic of UIHC for food and transportation insecurity and then connect patients with their community-specific resources to address those needs.

Since initiating this program in 2018, the Upstream Initiative has found that 17.7% of patients self-reported food insecurity (FI) during their initial visit while an additional cohort reported FI later in their pregnancy, bringing the total of patients identified as FI during their pregnancy to 20.4%. Designing interventions to best address FI and its impact upon health outcomes requires that we better understand FI patients' experiences, their gaps in utilization of available food resource programs, the chronicity and severity of household food insecurity, and the food choice impacts of FI.

**Objective:** To better understand our population of FI HROB patients, we sought to explore their severity of FI experienced, food resources currently accessed, barriers to utilization of food resources, likelihood to use potential new assistance programs, reported FI impact on household children, and additional social needs.

**Method:** Convenience sampling was performed of UIHC HROB patients between Jan 2022 and August 2022 utilizing a survey form of: a) either five (initial appointment) or three (subsequent appointment) FI questions, b) current use of specific food resources (SNAP/EBT/Food Stamps, WIC, food pantry, or food bank). Food insecure women, defined as acknowledging "yes" to any of the FI questions and/or to food resource usage, were then invited to complete an additional anonymous, numbered survey consisting of 27 items exploring their experience with FI. Patients were informed that this survey was confidential, anonymous, and voluntary. Survey data was entered and stored on Qualtrics.

**Results:** The 85 respondents were primarily white (74%), non-Hispanic (94%), currently married (42%), high school educated (40%), and reported income less than $20,000 per year (38%). About 10-15% of respondents reported cutting meals, eating less than they should, or not eating due to financial concerns. WIC (83%), followed by SNAP (61%), were the most common food assistance programs utilized. Among respondents with children in the house, 28% reported relying on lower-cost foods due to financial constraints, and 13% reported not being able to feed their children healthier meals due to affordability. The majority of respondents (51%) said they would be likely or very likely to utilize a food "prescription" program that provides fresh vegetables weekly from local farms.

**Conclusion**: Our study provides a more comprehensive view of the lived experience of the FI HROB clinic population at UIHC, their current community- based resources utilized, the impact of FI in pregnancy on the household, and the acceptability of potential interventions. The limitations of this study include a small sample size with reliance on volunteers to distribute the survey. Although an anonymous survey, the sensitive nature of the questions, particularly regarding impacts upon children in the home, could create response bias. Further, the self-reported concept of "healthy eating" was queried as opposed to an objective formal food intake assessment. Finally, the single-site and largely White, Non-Hispanic population limits generalizability of results to other groups. Future studies should explore food insecurity by both qualitative methods identifying barriers and facilitators to resource utilization, as well as a trial of a food prescription program with assessment of its impact on this population's health outcomes.

**The Hemodynamic Changes Associated with High Spinal Anesthesia in Infants Undergoing Cardiac Surgery**

Student: Aravinthasamy Sivamurugan, M2
Mentor: Satoshi Hanada, MD
Collaborators: Rakesh Sondekoppam Vijayashankar, MBBS

High spinal anesthesia (HSA) is a technique where a high-dose local anesthetic, such as bupivacaine, is intentionally administered intrathecally to achieve a high level of dermatomal blockade, usually above the cervical dermatomes. HSA is seldom combined with general anesthesia (GA) in patients undergoing cardiac surgery due to concerns of hemodynamic instability due to spinal anesthetic induced sympathectomy in the context of the underlying cardiac disease and general anesthesia. While there are concerns of hemodynamic instability with HSA in cardiac surgery patients, several reports seem to suggest that HSA may improve postoperative recovery. One reason for the lack of popularity of HSA in these patients is that the precise hemodynamic changes associated with HSA have never been investigated. At the University of Iowa Hospitals and Clinics (UIHC), HSA has been utilized in pediatric cardiac surgery to achieve faster patient recovery times as part of the fast-track strategy, but this practice is mainly practitioner dependent. We predicted that due to the underdeveloped autonomic nervous system in infants, there would be minimal hemodynamic effects with HSA. Therefore, we aimed to show the hemodynamic differences between infants who received HSA with GA and infants who received GA alone.

A retrospective database review was conducted to search for all pediatric patients between 1 month and 12 months old who underwent cardiac surgery between November 2011 and November 2021 at the UIHC after obtaining approval of institutional review board (IRB number 201911151). Intraoperative minute-to-minute hemodynamic data was extracted from patient charts including 10 minutes before and 60 minutes after anesthesia induction. Patients who received procedures of RACHS-1 (risk adjustment for congenital heart surgery) score greater than 3 were excluded since they are not candidates for the fast-track strategy. The remaining patients were divided into those who received HSA in combination with GA (HSA group) and those who received GA without any neuraxial blocks (GA group). A total of 202 infants were included in the final analysis, with 51 in the HSA group and 151 in the GA group. The primary outcomes of the study were differences in mean arterial pressure (MAP), heart rate (HR), and systolic blood pressure (SBP) after anesthesia induction between the two groups. Secondary outcomes included pressor usage after anesthesia induction, 30-day mortality, and 1 year mortality. The mean, minimum, and maximum of each of the MAP, HR, and SBP were also compared between the two groups. Additionally, the percentage change between the baseline and postinduction MAP, HR, and SBP were compared. Normality of the primary and secondary outcome variables was assessed by the Shapiro-Wilk test and construction of Q-Q plots. Statistical tests of significance were used to assess differences between the two groups. Multiple linear regression analyses including covariates such as age, sex, weight, surgery type, surgeon, and anesthesiologist were performed on each of the primary outcome variables.

The results showed no statistically significant differences in average post-induction MAP between the HSA and GA groups [Mean difference (95% CI ) = 0.9 mmHg [-4.9, 6.7] p =0.7482]. The difference between average postinduction HR in the two groups was statistically significant [Mean difference (95% CI ) = -9.2 bpm, 95% CI (4.4, 14.1) p=0.0001]. The average postinduction HR in HSA and GA were 129 and 138, respectively. Although this result is statistically significant; it may not be clinically significant since both values are within acceptable ranges for the age group. The differences in mean SBP were not statistically significant [Mean difference (95% CI ) = -7.8 mmHg, 95% CI (-0.6, 16.2) p=0.06262]. The difference in average percent decrease from baseline of MAP in both groups was not statistically significant at [Mean difference (95% CI ) = -4.3% 95% CI (-4.7, 13.4) p = 0.2877]. The regression analyses found that HSA did not predict changes in MAP or SBP but did predict changes in HR although, the change in HR was more affected by age as a covariate than HSA. Analysis of the secondary outcomes found no statistically significant differences in 30-day mortality, 1 year mortality, or intraoperative pressor use.

The use of HSA with GA in infants undergoing cardiac surgery produces comparable hemodynamic outcomes as GA alone. The profiles of MAP and SBP were equivalent between the two groups, however there was a statistically significant decrease in HR associated with HSA but well within clinically acceptable limits. These conclusions suggest that the hemodynamic safety of HSA with GA is comparable to GA alone in infants receiving cardiac surgery at the UIHC. Further prospective trials are warranted to verify these findings.

**Project title:** Sepsis is associated with an extended pro-inflammatory cytokine response compared to a critically-ill control

**Student:** Isaac Slagel, BA
**Mentors & Collaborators:** Patrick McGonagill, MD, Colette Galet, PhD, Vladimir Badovinac, PhD

## BACKGROUND

While there have been vast improvements in the diagnosis and clinical management of sepsis over the last 20-30 years, it remains a significant public health burden – striking 1.7 million Americans annually. It is estimated that sepsis is associated with 30% to 50% of all in-hospital mortalities. While the immune response to sepsis remains variable among individuals, patients who survive sepsis often display prolonged immunoparalysis, which dramatically increases the susceptibility to secondary infection. Since 2018, Dr. McGonagill, MD (clinical mentor, Acute Care Surgery Division, Department of Surgery) has established a collaboration with Dr. Badovinac, PhD (Department of Pathology) to further elucidate the cellular mechanisms underlying sepsis-related immunoparalysis. By analyzing clinical outcomes alongside cytokine data, we aimed to better characterize risk factors for poor outcomes and gain a deeper understanding of the immune response during sepsis by comparing septic patients to patients who are critically ill non-septic (CINS).

## STUDY AIMS

1) Identify clinical markers of immune dysfunction which predict poor outcomes in septic patients.
2) Develop a deeper understanding of septic immunoparalysis in comparison to immune system metrics of CINS control patients.

## METHODS

**Sample collection and cytokine assays**: Blood samples were collected within 24 h of presentation for septic and critically ill non septic (CINS) patients as well as at day 3 ± 1, 7 ± 1, 14 ± 2, 21 ± 2, and 30 ± 5 days. Cytokines were measured using the R&D Systems Human Lumniex Discovery Assay (#LXSAHM-19).
**Data collection and analysis**: Clinical data were collected in a REDCap database retrospectively. Summary statistics were obtained describing our CINS and septic populations using chi-square and two-sample t-tests. Mann-Whitney U tests were performed to assess differences in cytokine levels between the CINS and septic groups. Multivariate analysis was performed to identify associations between markers of immune dysfunction and mortality and ICU length of stay in septic patients. All statistical analysis was be performed using R version 4.1.3 with $P < 0.05$ considered significant.

## RESULTS

Data were collected on 207 patients. Patients with less than 7 days of data and those who crossed over between sample groups were excluded. The study sample included 92 patients, 61 in the sepsis cohort and 31 in the CINS cohort. On average, our septic cohort was significantly older (62.6 ± 14.9 vs. 49.2 ± 19.2y; p =0.002) and presented significantly higher Charlson scores on admission (3.3 ± 2.2 vs. 1.8 ± 2.1; p = 0.003). Septic patients stayed significantly longer in hospital (18.2 ± 10.8 vs. 14.6 ± 6.7 days; p =0.033) and had higher, but not significantly different, rates of mortality (11.5% vs. 0%, p = 0.122). On admission, septic patients had significantly higher levels of TNF-α, IL-17, and CXCL10 than CINS patients (22.2 vs. 17.6, p <0.001; 52.8 vs. 47.4, p = 0.011; and 104.4 vs. 71.5, p = 0.013, respectively). Over 7 days, levels of S100A8 and CRP declined in CINS patients, while those increased in septic patients (-21% vs. 25%, p =0.003 and -13% vs. 27%, p <0.001, respectively). Multivariate analysis controlling for baseline characteristics did not yield any significant results as it was underpowered due to the high variability in cytokine levels and outcome data.

## CONCLUSION

Our exploratory analysis illustrated differences between septic and CINS patients and could provide deeper insight into the immune dysfunction present in sepsis and identify treatment targets. Our results depict greater immune dysfunction within the septic population, as expected. While serum cytokine values did show the dysregulated immune response characterized by sepsis, confounding variables from the clinical setting and variability in cytokine levels obfuscate clear and significant differences between septic and CINS patients. Future work is warranted to better understand how to standardize patient's timeline of illness when presentation for treatment can vary drastically.

# Trending Ability of Cardiac Output Measurement by LiDCO Rapid™ and Transesophageal Echocardiography in Elective Cardiac Surgery: A Comparison with Thermodilution

Snyder, Olivia MS-4; Sagar, John; Hanada, Satoshi, MD; Subramani, Sudhakar MD,FASE

Background – Measurement of cardiac output (CO) is considered an important hemodynamic parameter in cardiac surgery. The current gold standard for CO measurement, the pulmonary artery catheter (PAC), has come into question in regards to its safety and efficacy. A replacement for the PAC in the intra-operative setting would be an advancement in safety in an already high-risk setting. Over the past decades, less invasive techniques and monitors such as transesophageal echocardiography (TEE) and LiDCO™ have been developed as alternatives to the PAC. We compared the ability of the LiDCOrapid™ and TEE to measure CO directly and also the trending ability of these devices to that of the PAC.

Methods – 100 patients undergoing elective cardiac surgery were enrolled for this prospective observational study. There was no change in the routine anesthetic care. We measured CO at five times during the study period: immediately after induction, five minutes after placing in Trendelenburg position, immediately after incision, 15 minutes after weaning from bypass, and after chest closure. The specific values from the first and last readings of each device were compared to each other and sorted into good (difference <30%) or poor correlation (difference >30%). Polar plot analysis was performed to measure trending ability of each monitor and radial limits of agreement (RLoAs) within ±30° were considered as acceptable error at any quadrant.

Results – Overall 1500 data points in 100 subjects were analyzed. Only 24 subjects showed good relation between all three devices at the after induction measurement, and 41 out of 100 from the post-chest closure measurement. Except for preoperative EF (P=0.006) and HR in post-chest closure (P=.04), none of the demographic and clinical conditions showed a statistically significant difference between good and poor correlation. The Bland-Altman plot for PAC v. LiDCO showed limits of agreement (LoA) of 4.5 L/min and -3.1 L/min with a mean difference of .7L/min, PAC v. TEE showed LoAs of 5.4L/min and -2.7L/min with a mean difference of 1.2L/min. Trending ability after excluding cardiac output difference <0.5L/min showed poor correlation with LiDCo and TEE in comparison with PAC.

Conclusions – Both LiDCO Rapid™ and TEE correlated poorly with the PAC. Both devices showed limit of agreement well outside the limit when compared to PAC, showing poor trending ability, therefore should not be considered as a suitable alternative monitoring tool during cardiac surgery.

# After the Storm: Post-Viral Neuropathies in COVID-19 and Influenza

Sadie Lusskin Solomon, BS; Beth Dinoff, PhD; Aloha Wilks, CPC; Martha L. Carvour, MD, PhD

**Background:** The COVID-19 pandemic has had a broad impact on national health. Many patients report lingering symptoms after an acute COVID-19 infection. These symptoms are called post-acute sequelae of SARS-CoV-2 infection (PASC). PASC can include fatigue, dyspnea, cognitive changes, and painful neuropathies that can last for months or years after the acute COVID-19 episode. The prevalence of PASC neuropathies is not well established; and there is limited epidemiological evidence about how the prevalence and underlying causes of these neuropathies compare to those in other post-viral syndromes.

**Purpose:** The aims of this study were to estimate the prevalence of pre-viral and post-viral neuropathies for COVID-19 and influenza using a large, multi-center dataset and to determine whether post-viral neuropathies were more common among patients with diabetes, a known prevalent cause of neuropathy.

**Methods:** A cohort of over 1 million patients diagnosed with either COVID-19 or influenza was assembled using TriNetX electronic medical record data from more than 40 hospital systems across the United States. Neuropathy and diabetes were defined using International Classification of Diseases codes (versions 9 and 10) through expert review by a multidisciplinary group with clinical experience in pain, infectious diseases, internal medicine, and professional coding. Patients with COVID-19 were diagnosed between 1/1/2020 and 7/31/2021. Patients with influenza were diagnosed between 1/1/2018 and 7/31/2019. Pre-viral neuropathy was defined as any diagnosis before the acute viral diagnosis and up to 14 days after, and post-viral neuropathy was defined as a new diagnosis more than 14 days after the acute viral diagnosis. Post-viral neuropathies were included if these occurred within 6 months after the last date of diagnosis for the cohort (1/31/2022 for COVID-19; 1/31/2020 for influenza), which allowed for a variable length of follow-up within the cohort. The prevalence of pre-viral and post-viral neuropathy was calculated for both COVID-19 and influenza. Results were stratified by diabetes status. Post-viral neuropathies were compared using Kaplan-Meier and proportional hazard regression analyses in SAS 9.4.

**Results:** The cohort consisted of 828,557 COVID-19 patients; 260,256 influenza patients; and 12,594 patients had influenza and subsequent COVID-19 during the eligible study windows. In the COVID-19 cohort, 114,360 (14%) had a pre-viral neuropathy, compared to 34,574 (13%, $p<0.0001$) patients in the influenza cohort. In addition, 153,136 (19%) COVID-19 patients had pre-viral diabetes, compared to 40,126 (15%, $p<.0001$) influenza patients. Post-viral neuropathies rose slowly but steadily in both groups, with the influenza cohort exhibiting a 57% higher rate of diagnosis (HR 1.57, 95% confidence interval: 1.50 – 1.61, $p<.0001$). As expected, patients with pre-viral diabetes had a higher rate of post-viral neuropathy diagnosis compared to those without pre-viral diabetes in both cohorts.

**Discussion:** In this large, multi-center cohort, patients with COVID-19 had a higher observed prevalence of *pre*-viral neuropathies compared to patients in the influenza cohort. This may reflect differences in underlying comorbidities. For instance, as expected, the COVID-19 cohort also had a higher rate of pre-viral diabetes. By contrast, the influenza cohort had a higher rate of *post*-viral neuropathies compared to the COVID-19 cohort. It is unclear whether this reflects a true difference in risk, a difference in diagnosis rates (i.e., underdiagnoses or missed diagnoses related to pandemic-era disruptions in care), or another difference resulting from underlying, confounding risk factors. Subsequent epidemiological analyses in this dataset and others, including risk stratification, multivariable analyses, and bias assessments, are needed to elucidate the distribution and determinants of PASC neuropathies. As anticipated, patients with diabetes in both cohorts had higher rates of post-viral neuropathies compared to those without diabetes. This finding supports ongoing adherence to evidence-based guidelines for neuropathy prevention and assessment in patients with diabetes, including patients with a recent viral diagnosis.

**Title:** The temporal association and differential decrease of depression symptomatology between 10 Hz repetitive transcranial magnetic stimulation (rTMS) and intermittent theta burst stimulation (iTBS)

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**Background:** Transcranial magnetic stimulation (TMS) is a novel, FDA-cleared neuromodulation treatment for major depressive disorder. TMS treatment strategies include the standard of care 10 Hz repetitive TMS (rTMS) and a newer FDA-cleared modality, intermittent theta burst (iTBS) -- recently demonstrated as non-inferior in 2018. At present, few studies exist that have examined a differential depression symptom response to TMS treatment, and no studies to our knowledge, have further analyzed for differences between the two TMS treatment modalities.

**Purpose:** Our study sought to explore if certain depression symptoms improved faster than others after TMS treatment and to examine differences between trajectories of symptom improvement with iTBS and 10 Hz rTMS.

**Methods:** We performed retrospective analyses of participants with MDD that received open-label TMS treatment at the left dorsolateral prefrontal cortex (DLPFC) to examine response to treatment using weekly Patient Health Questionnaire 9 (PHQ-9) scores [10 Hz rTMS (n=68) and iTBS (n=37)], as well as pre, mid, and post-treatment Montgomery–Åsberg Depression Rating Scale (MADRS) scores [10 Hz rTMS (n=65) and iTBS (n=28). Using cumulative logistic regression analyses, and pairwise odd ratio point and interval estimates, effects between treatment group and treatment number at weekly intervals were used to investigate if specific depression symptoms responded differentially.

**Results:** PHQ-9 scores amongst TMS responders (>50% improvement on PHQ-9, n=41) showed rapid and significant improvement in most items in one week of treatment, but a slower improvement on item #6 “feeling bad about yourself” (at week 3, $p = 0.046$) and on item #8 psychomotor changes (at week 5, $p = 0.0031$). Investigating differences between 10 Hz rTMS and iTBS using the weekly PHQ-9, we found 10 Hz rTMS showed greater response for item #2 “feeling down, depressed, or hopeless” at week 6 of treatment ($p = 0.045$); as well as for item #4 “feeling tired or having little energy”, with 10 Hz rTMS having a significantly greater reduction from baseline, compared to iTBS ($p = 0.027$). MADRS scores between 10 Hz and iTBS responders showed faster response in the 10 Hz rTMS group on symptoms of “reported sadness” (item #2) and “lassitude” (item #7) from baseline to the mid-treatment time interval ($p = 0.0320$ and $p = 0.0060$, respectively). There were no other depression symptoms that had a significantly different response pattern between the two modalities.

**Conclusion:** Using PHQ-9 and MADRS depression rating scales, we found TMS treatment responders demonstrated more gradual improvements in pessimistic thinking and psychomotor abnormalities compared to other depressive symptoms. 10 Hz rTMS showed faster response in symptoms of reported sadness and lassitude, as well as trended towards a faster response in other symptom categories compared to iTBS. We did not find a significant difference between 10 Hz rTMS and iTBS in overall response rates at completion of treatment. Delineating the temporal trajectory of depression symptom improvement and differences between TMS modalities may enable clinicians to tailor treatment strategies and further guide patient expectations in relation to specific symptoms of depression.

## Longitudinal symptom tracking of Long-COVID

Grant Stalker, Dr. Alejandro Pezzulo

Johns Hopkins Coronavirus Resource Center reports that the COVID-19 pandemic has resulted in over 74 million confirmed cases and almost 900,000 deaths to date in the United States alone. COVID-19 infections are widely variable from person to person with outcomes ranging from no symptoms to death. Current estimates put the fatality rate at ~0.5% with a significant portion of those infected experiencing long-term disability to due to severe disease. These symptoms include persistent respiratory issues, prolonged loss of taste and smell, and a new or worsening ability to complete the activities of daily living after recovering from a severe COVID-19 infection. To date, the chronology of long-COVID has been poorly described with no current research fully characterizing the time course of the disease. Our research looked to better elucidate the symptom chronology and subjective patient experience of long COVID. The overall hypothesis for this research is that the clinical characteristics of patients affected by acute COVID19 will impact the patient's experience of Long COVID.

This study used both a survey generated by our research group and chart review to collect data. The University of Iowa previously established a long-COVID clinic where patients were enrolled in a registry for follow up. Over 450 patients since June 2020 have consented to participate in the research registry and have provided standardized data including symptoms during acute illness, symptom progression, serum biochemistry, inspiratory and expiratory computed tomography chest imaging, pulmonary function testing, and other clinical characteristics. We sent all patients in this registry our survey containing questions about vaccine status, reinfection status, current symptoms, and patients' subjective experience of improvement (sliding scale, 0 being worse, 50 being no change, 100 being fully recovered) from long-COVID. Patient's who responded to the survey over a year after their diagnosis had further chart review done to track their symptomology from the time of their acute COVID19 infection to their survey response using office visits, emergency room visits, and hospital visits to track symptoms. Persistent symptoms were defined as reported symptom during their acute COVID infection and the first mention of dyspnea at a follow up visit was also positive for dyspnea.

129 patients who previously consented to participation in the University of Iowa's long-COVID registry responded to our survey. The age breakdown (in years) of our cohort was as follows: 18-29 (10.1%), 30-39 (12.4%), 40-49 (27.13%), 50-59 (26.36%), 60-69 (15.5%), and 70+ (8.53%). 31.8% of the cohort was male and 68.2% of our cohort was female. The severity of acute covid treatment was stratified by treatment in the outpatient (70.5%), inpatient (16.3%), or ICU (13.2%) settings. Overall, 51.2% of patients reported significant subjective improvement (sliding scale scores of 67-100), 40.3% reported little or no subjective change (sliding scale scores of 33-66), and 8.5% reported feeling subjectively worse (sliding scale scores of 0-32) than when they first experienced long-COVID. Patients in the age 18-29 group reported significantly higher subjective improvement scores, with every respondent in this age group reporting subjective improvement from the time they initially experienced long-COVID to the time of their response. No other age group differed significantly. Males and females reported similar subjective improvement and the subjective improvement scores did not vary based on acute COVID care. 48 respondents reported persistent dyspnea and 23 (48%) reported no dyspnea by their follow up visit. 44 respondents reported persistent fatigue and 12 (27%) reported no dyspnea by their follow up visit.

Within on our cohort, young age (18-29) was a significant factor in patient's subjective recovery from long COVID. Every respondent within this group moved their sliding scale to the "better" category. Dyspnea and fatigue were the most common reported symptoms and most bothersome symptoms reported. This data suggests that those who suffer from persistent dyspnea have an approximately 50% chance of recovering from the disease at or past the 1-year time point. Fatigue seems to be more long-standing, with only 27% of patients fully recovering from their acute COVID fatigue. This data suggests that the time course of long-COVID recovery may extend past 12 months for most patients experiencing persistent symptoms. Further, the time course of recovery may differ for patients experiencing certain symptoms. A logistical regression model still needs to be applied to our data set to account for potentially confounding factors. One limitation of this study is the interpretation of respondents to our health improvement questions. Some respondents may have interpreted the question as asking about how their health compares to their acute COVID infection which would impact their scores. An additional limitation is that the symptom tracking done through chart review was not standardized. Various physicians and hospital locations were used to collect data and the definition of certain symptoms may vary between these entities impacting reporting of said symptom. Overall, a more standardized study with defined time points for each patient is needed to better characterize the true course of long-COVID symptomology.

***Somatic growth outcomes in response to a neonatal sodium supplementation protocol***

Elliot J. Stalter, Silvia L. Verhofste, Jeffery L. Segar, John M. Dagle, Patrick Ten Eyck, Linder Wendt, Emily J. Steinbach, Lyndsay A. Harshman

**Background**

Preterm infants are susceptible to total body sodium depletion. This is associated with impaired somatic growth. An individualized sodium supplementation protocol was established at the University of Iowa Stead Family Children's Hospital Neonatal Intensive Care Unit (UISFCH NICU) in 2016 based upon standardized urine sodium screening. Pilot data from this protocol demonstrated increased weight gain within the first 8 weeks of life among infants receiving sodium supplementation compared to historical controls. We performed a retrospective cohort study of 692 infants born between 26 0/7 and 33 6/7 weeks gestation treated within the UISFCH NICU between 2012 and 2020 to evaluate long-term growth and protocol safety.

**Purpose**

Our primary aims were to 1) evaluate the short- and long-term growth trajectories of preterm infants who received enteral sodium supplementation according to the sodium supplementation protocol, 2) identify potential adverse health outcomes associated with the protocol, and 3) validate previously collected pilot data within a broader NICU cohort.

**Methods**

Total body weight, body length, and head circumference were obtained for 225 sodium-supplemented and 157 un-supplemented infants born between 26 0/7 and 29 6/7 weeks gestation and 157 sodium-supplemented and 153 un-supplemented infants born between 30 0/7 and 33 6/7 weeks gestation. Growth parameters were examined at birth and 2-, 4-, 6-, 8-, 16-, 26-, and 36-weeks postnatal age. Within- and between-group changes over time were assessed using repeated measures generalized linear modeling controlling for gestational age, sex, and birthweight. The incidence of hypertension, hypernatremia, total time on mechanical ventilation, and time to discharge were compared between the sodium supplemented and un-supplemented cohorts.

**Results**

For the 26-29 weeks gestation cohorts, sodium supplementation was associated with greater average weight gain at 26- and 36-weeks postnatal age ($p = 0.0028$ and 0.0143, respectively). Sodium supplementation was associated with decreased time on mechanical ventilation ($p = 0.0076$) and was not associated with development of hypertension ($p = 0.8345$). Sodium supplementation was associated with decreased risk of developing mild hypernatremia (146-149 mEq/L; $p = 0.0031$) but not moderate hypernatremia (150-169 mEq/L; $p = 0.1928$). For the 30-33 weeks gestation cohorts, sodium supplementation was not associated with greater average weight gain at any timepoint. Average time to discharge was increased in both 26-29 and 30-33 weeks gestation sodium supplemented cohorts ($p = 0.0038$ and 0.0001, respectively).

**Discussion**

Extremely preterm infants receiving protocol-based, enteral sodium supplementation demonstrated better early-life weight gain compared to un-supplemented historical controls without serious adverse events attributable to receipt of enteral sodium supplementation.

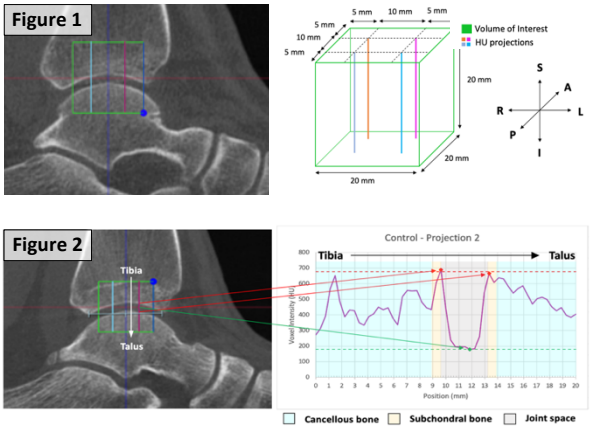
**DEFINING NORMAL ARTICULAR CHARACTERISTICS OF THE PRIMARY JOINTS OF THE FOOT AND ANKLE: A 3D HOUNSFIELD ALGORITHM WEIGHT BEARING CT STUDY**

Hannah Stebral, BS; Cesar de Cesar Netto, MD, PhD; Donald D. Anderson, PhD.

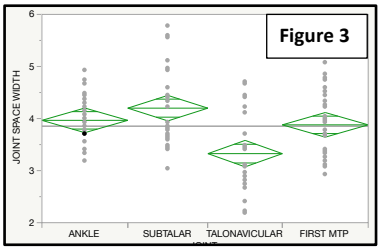
**Background**: There are four primary articulations in the foot and ankle that enable its great range of motion and support gait. They are the tibiotalar (ankle), subtalar (ST), talonavicular (TN), and 1st metatarsophalangeal (MTP) joints. These four articulations are also frequently subject to degenerative osteoarthritis (OA). To properly treat OA patients, a grading system is used to diagnose the stage of the disease. The current gold-standard system, which relies on plain 2D radiographs, is subjective, categorical, and lacks reliability. Weight bearing CT (WBCT) scans now provide 3D imaging assessments of foot and ankle joints under physiological upright load bearing conditions that can be used to more accurately assess OA degenerative changes. Using WBCT images, 3D Hounsfield Unit (HU) algorithms have been developed to measure the intensity of each image voxel across the joint space, highlighting transitions between cancellous/subchondral bone and joint space. These HU line intensity profiles across each joint afford new measures of joint space width (JSW) and bone quality distribution. Defining normal joint space characteristics of the different joints of the foot and ankle is important to set standards, and to allow development of a more objective, accurate and reliable OA staging system.

**Purpose**: The purpose of this study was to analyze and define normal standard values of JSW in the four essential joints of the foot and ankle (ankle, ST, TN, and 1st MTP joints) using an objective computational WBCT HU algorithm in healthy non-arthritic feet. We hypothesized that the measurements of JSW and HU distributions across each of the four essential joints of the foot and ankle would be significantly different from each other, respecting local anatomy and unique functional characteristics of each joint.

**Methods**: In this retrospective IRB-approved comparative study, we evaluated WBCT scans of 30 healthy ankle joints, 28 ST joints, 26 TN joints, and 30 1st MTP joints of control volunteers with no radiographic signs of foot and ankle OA. For each joint, we used dedicated software to define a volume of interest (VOI) cube centered on the joint space. Five HU linear search arrays were then defined within this 3D VOI perpendicular to the articular surface of each joint, including four projections in each quadrant, and one in the center of the VOI (Figure 1). Image intensity profiles were generated for each search array crossing the transition from cancellous to subchondral bone, across the joint space, back to subchondral and cancellous bone (Figure 2). This profile was used to calculate JSW and to measure HU contrast in the region. To calculate JSW, the two maximum intensity values ($I_{max1}$ and $I_{max2}$) on the plot were first manually selected. Then the distance along the X-axis between these two maxima was found. When scaled by the WBCT spatial resolution, this equates to the JSW. Each joint thus had 5 different JSW measurements made over the VOI. The median of these 5 values was used to define the JSW for that specific joint. To calculate the HU (Michelson) Contrast, first the $I_{max,avg}$ was calculated by finding the average of $I_{max1}$ and $I_{max2}$. Next, the following formula was used: $(I_{max,avg} - I_{min})/(I_{max,avg} + I_{min}) * 100$. Data Normality was analyzed by Shapiro-Wilk Test. Comparisons between the JSW of each joint and within each joint were accordingly performed using paired t-tests or paired Wilcoxon. Significance was considered for p-values <0.05.




**Results**: The median value and 95% Confidence Intervals (CI) for JSW were 4.07 mm [CI: 3.73 – 4.20] for the ankle joint; 4.07 mm [3.95 – 4.44] for the ST joint; 3.24 mm [3.19 – 3.46] for the TN joint; and 3.70 mm [3.64 – 4.12] for the 1st MTP joint. The TN JSW was significantly narrower than the JSW in the ankle (p=0.0007), ST (p<0.0002), and 1st MTP (p=0.0034) joints (Figure 3). Ankle, ST and 1st MTP joints were not significantly different from each other. JSW values were similar across the entire ankle, ST and 1st MTP joints. In the TN joint, the dorsal aspect of the joint was found to be slightly but significantly wider than the plantar aspect (p<0.001). Regarding HU contrast, we found a progressive increase in the overall contrast from proximal to distal (p<0.001), with a mean HU contrast value and 95% CI of respectively 71.8 [67.3 – 76.3] for ankle, 92.4 [87.8 – 97.1] for ST, 84.1 [79.2 – 88.9] for TN, and 101.3 [96.9 – 106.8] for 1st MTP joints. The only joints with similar HU contrast were ST and TN.




**Conclusions**: In this study we utilized a novel WBCT 3D HU measurement algorithm to assess the normal JSW and HU contrast of the four essential mobile joints of the foot and ankle. We found the JSW to be similar (~4mm) in the ankle, ST, and 1st MTP joints. The TN joint however, demonstrated a significantly narrower JSW when compared to the other 3 joints. HU contrast increased progressively from proximal to distal, being less prominent in the ankle, similarly increased in TN and ST, and maximum at the 1st MTP joint. The joint characteristic normality data presented in this study provide a foundation for future work developing an objective WBCT-based 3D HU algorithm staging system for OA disease progression in the foot and ankle joints.

**The effect of *in vivo* and *in vitro* preeclamptic conditions on cardiovascular measures and phenotypes**

Hannah Sullivan, MS2
Brandon Schickling, PhD
Mark Santillan, MD, PhD

**Background and Purpose**: Preeclampsia is a prevalent gestational disorder characterized by hypertension, proteinuria, and renal damage. Preeclampsia is the leading cause of worldwide obstetric mortality with 76,000 maternal and 500,000 neonatal deaths per year. Additionally, patients with a history of preeclampsia are at increased risk of future cardiovascular complications (CVD) including myocardial infarction and stroke as well as vascular disease such as chronic hypertension and atherosclerosis. Despite the prevalence and severity of these long-term effects, little is understood about the mechanisms that cause the increased risk of future CVD. The purpose of this study is to investigate the effects of various preeclamptic models on elements of the cardiovascular system.

**Methods**:
*Mouse Model*: Using an established preeclampsia mouse model, pregnant and non-pregnant reproductive aged (10-14 weeks) female mice were chronically infused with either saline or arginine vasopressin (AVP). Pregnant mice were sacrificed at GD 18. Blood pressure was measured throughout pregnancy and heart weights were measured at sacrifice. Hearts were analyzed for expression of genes of interest using qPCR.

*Plasma/cell culture:* Human 3$^{rd}$ trimester maternal plasma samples (matched by gestational age and BMI) were obtained from the Iowa Maternal Fetal Tissue Bank (IRB# 200910784). Levels of brain natriuretic peptide (NT-ProBNP) and atrial natriuretic peptide (MR-ProANP) were measured for a case control study. H9C2 rat cardiomyocytes were treated with pooled plasma from patients with and without preeclampsia (5%). Additionally, aortic smooth muscle cells (SMCs) were extracted from pregnant female mice and treated with both plasma conditions (5%). Expression of genes of interest was measured using qPCR. Cell counts were obtained using the IncuCyte S3.

**Results:** AVP infusion during mouse pregnancy was shown to cause a *pregnancy specific* increase in mean arterial pressure as well as average heart weight ($p=0.011$) when compared with saline. There was also a significant pregnancy specific increase in markers of fibrosis (Col1a1 $p=0.016$, Col1a2 $p=0.035$, Col13a1 $p=0.019$) and levels of NT-ProBNP ($p=0.013$). In the plasma samples from patients with preeclampsia, there were significantly higher levels of NT-ProBNP and MR-ProANP ($p=0.001$, $p=0.017$) compared to pregnant patients without preeclampsia, illustrating a clinically relevant increase of cardiac stress. Additionally, treatment of H9C2 rat cardiomyocytes with pooled plasma from preeclamptic patients showed a 6.6 and 1.83 fold increase in rat ANP and BNP expression respectively compared to cells treated with normal pregnancy plasma. Further, treatment with plasma from preeclamptic patients caused mouse aortic smooth muscle cells to express significantly reduced levels of smooth muscle cell gene expression (ACTA2 $p=0.004$, Myh11 $p=0.015$) compared to treatment with normal plasma. Treatment with preeclamptic plasma also induced an 8.1 fold increase in cell proliferation compared with non-preeclamptic patient plasma.

**Discussion:** Overall, results from the cardiac measures indicated increased levels of cardiac hypertrophy and fibrosis under preeclamptic conditions. Results from aortic smooth muscle cell experiments indicated two concurrent processes- dedifferentiation and proliferation. When smooth muscle cells undergo dedifferentiation, they phenotypically switch from a quiescent differentiated state to an activated state. Dedifferentiation and proliferation are well understood components of neointimal hyperplasia, a change that precedes many types of vascular disease. Taken together, these data suggest that circulating factors in preeclamptic patients are in part contributing to cardiac hypertrophy, cardiac fibrosis, SMC dedifferentiation, and SMC proliferation; all of which are important components of cardiovascular disease. Further work will explore the potential circulating factors in the plasma that lead to these changes.

**A one-year prospective study of all delivering women at a Midwest academic health center**

Student: Samantha Swartz, BS
Mentor: Brooks Jackson, MD, MBA
Collaborators: Kimberly Kenne, MD, MCR, Linder Wendt, MS, Mary Rysavy, MD

**Introduction:** The landscape of obstetric care in Iowa has changed in recent years due to closure of rural labor and delivery services. The University of Iowa Hospitals and Clinics (UIHC) serves as a referral center for the state and has seen increased delivery volumes as a result of nearby closures. At the same time, maternal characteristics are also shifting. The pre-pregnancy BMI of reproductive-age women is increasing nationally, a trend which is reflected in Iowa. In addition, maternal age at first delivery is increasing both state-wide and nationally. Increased delivery volumes and changing maternal characteristics have likely altered the population of patients served by UIHC.

**Objectives:** The aim was to characterize and describe the outcomes of the delivering population at UIHC over a one-year period to better understand the population we serve, as well as compare our population to state and national delivering populations.

**Methods:** This prospective study included all pregnant patients who delivered at UIHC between May 1, 2020, and April 30, 2021. Demographic and clinical data including maternal characteristics, delivery information, maternal complications, and neonatal outcomes were obtained from the electronic medical record and double entered in a Research Electronic Data Capture (REDCap) database. Continuous variables were summarized using medians and inter-quartile ranges (IQR), while categorical variables were summarized using counts and percentages. Obesity and cesarean section rates were compared to national averages via a one-sample exact binomial test.

**Results:** The median maternal age among the 2,499 mothers included in the study was 30 (IQR 26-33). The median BMI was 31.8 (IQR 27.9-37.6), 1,769 (70.8%) patients were White, and 2,275 (91.0%) listed English as their preferred language. The mothers delivered a total of 2,606 babies, with 2,394 singleton births, 103 sets of twins, and 2 sets of triplets. Of the total deliveries, 2,543 (97.7%) were live births. Among the live births, 892 (35.1%) were born by cesarean section vs. 1,558 (64.9%) born by vaginal delivery. Of vaginal deliveries, 124 (7.4%) were forceps- or vacuum-assisted. 467 (18.7%) of deliveries were preterm, with term delivery defined as 37w0d or later in gestation. The median birth weight was 3,240 g (IQR 2,800-5,275 g), with 433 (16.6%) neonates born at low birth weight (<2500 g).

**Discussion:** On average, delivering patients at UIHC were older than delivering patients across the United States. The average maternal age of primigravid women in our population (29.6) was higher than the national average of 27.1 years. The cesarean section rate at our institution was 35.1%, which is higher than the national rate (31.8%) by a statistically significant margin ($p = 0.0017$). This high rate of C-section could be due to a large volume of complicated pregnancies.

**Conclusion:** The UIHC delivering population is greater than 88% overweight or obese. Our population is also older and delivers via cesarean section at a higher rate than the national delivering population.

**Metabolomic Profiling of Human Schwannomas and Meningiomas Before and After Radiation**

Hashim Syed, Mark Dougherty, Eric Taylor, Marlan Hansen

**Background**: Vestibular schwannomas (VS) and meningiomas account for approximately 10% and 37% of all primary intracranial neoplasms. Usually, these tumors can be treated with surgical resection and radiation. However, when those treatments fail no further options exist. Metabolomic profiling is a method in which the relative quantities of metabolites present in tissue samples can be demonstrated. However, few efforts have been made to characterize the metabolomic profile of schwannomas and meningiomas. Doing so could establish new techniques for prognostic and predictive analysis to be used as an additional factor in decision making, and therapeutic strategy.

**Hypothesis**: We hypothesize that 1) radiation induces specific metabolomic changes in meningiomas and schwannomas, and 2) these changes arise from alterations in targetable metabolic pathways.

**Methods**: Schwannomas and meningiomas were resected from consented patients at UIHC, and samples were subsequently collected. Part of each tumor sample was immediately flash frozen in liquid nitrogen for metabolic analysis and to serve as a non-xenograft control, with the remainder of the sample being segmented and implanted into nine nude mice under isoflurane anesthesia. Mice then received postoperative care in the form of Rimadyl pain medication and general checkups. At least four weeks post-implantation, MRI was used to confirm tumor implantation. Then, samples were randomized to either 10 or 20 gray (Gy) of ionizing radiation or received sham radiation treatment. 72 hours after treatment, the mice were anesthetized, and the implanted tumors were harvested. Following adequate tumor sampling, they were euthanized. To ensure accurate tissue sampling, sections of the harvested xenograft tumor were placed in preservative and sectioned for immunohistochemistry staining. For cell type identification, we used primary antibodies against epithelial membrane antigen (EMA) to label meningioma cells and S100 for schwannoma cells. Nuclei were stained with 4′,6-diamidino-2-phenylindole (DAPI). Tissue slides were prepared, with half of each slide receiving the appropriate primary antibody and the other half receiving empty blocking buffer to serve as a negative control. Secondary antibody was then applied to the entire tissue slide, and signal comparison between the two sides allowed for confirmation of tumor tissue. Additionally, the Click-iT EdU Proliferation Assay was used to measure tumor cell proliferation. This is used to validate the observed metabolomic changes as attributable to the effects of radiation and not another unknown variable. One day before tumor harvest, mice were injected with 5-ethynyl-2′-deoxyuridine (EdU) to allow for uridine analog incorporation into the implanted tumors replicating cells. Tissue was then stained on the tumor slides, and MetaMorph software was used to count the total number of cells. The proliferation rate was calculated as the number of EdU-stained cells (replicating cells) divided by DAPI-stained cells (total cells) averaged over 8 images per tumor. Finally, we prepared tissues for gas chromatography-mass spectroscopy (GC-MS) analysis by flash freezing samples in liquid nitrogen at the time of surgical resection and on mouse xenograft specimens. Samples were then stored in an enclosed container at -80C. Primary human leptomeningeal cells and Schwann cells were cultured according to iXCells Biotechnologies protocol, and after reaching confluence, cultures were also flash frozen in liquid nitrogen and stored at -80C.

**Results**: Due to batch effects from the Thermo Q Exactive GC-MS, many samples have not yet been sent for metabolomics analysis. So far, immunohistochemistry has been useful in confirming schwannoma xenografting success, as all stained schwannoma samples return a quantifiable difference in secondary antibody signaling. Meningioma staining has produced more variable results with certain samples returning a strong signal difference, while others have had near identical signal on both sections. We plan to perform hematoxylin and eosin (H&E) staining on these samples to confirm tumor morphology. EdU Cell proliferation data collection is ongoing but preliminary data is promising, showing a consistent trend where increasing radiation decreases cell proliferation rates. The average meningioma proliferation rate for the sham radiation group was $1.99 \pm 0.70$ SD, $1.39 \pm 0.90$ for 10 Gy, and $1.24 \pm 0.40$ for 20 Gy radiation. The average schwannoma proliferation rate was $3.24 \pm 1.93$ for 0 Gy, $3.01 \pm 2.11$ for 10 Gy, and $1.97 \pm 1.74$ for the 20 Gy radiation group. Finally, primary human Schwann cells were successfully cultured, passaged once, then split into 9 dishes which were flash frozen and are awaiting analysis.

**Conclusion**: Although work is ongoing, preliminary metabolomics data points to several potential metabolites and possible pathways that may be altered post radiation. As more metabolomics data is obtained, background noise will ideally be reduced allowing for stronger elucidation of the effects of radiation on the tumor metabolome. Once we can identify specific pathways and metabolites, we intend to begin isotope tracing using 13C-labeled Glutamine, which will allow for pathway mapping and analysis. Concurrently staining sections of tumor and executing EdU cell counts has allowed us to further validate the changes in metabolism as due to radiation and not an unknown variable.

# Identifying the Effects of Neuromodulation on Airway Repair

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Neurotrophins are a family of four peptide growth factors (NGF, BDNF, NT-3, NT4) understood for their roles in promoting neuron development and survival.[1-3] Each neurotrophin activates one of the Trk receptors (TrkA, TrkB, or TrkC) while simultaneously activating the pan-neurotrophin receptor, NGFR.[1,2] Activation of NGFR facilitates downstream activation of NF-KB, Akt, and JNK pathways, thus linking neurotrophin signaling to cell survival and the inflammatory response. Although neurotrophin receptors exist in multiple tissue types, the function of these neurotrophins remain undefined outside the nervous system.[1-3]

NGF, BDNF, and NT-3 are constitutively expressed by airway epithelia cells, but the airway response to neurotrophin activation is only minimally understood. There is evidence associating airway neurotrophin signaling with pro-inflammatory states. For example, both BDNF and NT-3 have been shown to drive severe asthma and COPD.[4,5] Multiple studies have observed neurotrophin receptor stimulation as promoting immune cell activation within the respiratory tract.[3,4] Furthermore, preliminary work from the Stoltz lab indicates TrkA overexpression in response to IL-13 treatment. We have also observed an increase in NGF expression, yet a decrease in NGFR levels, during airway epithelia repair.

This project aims to elucidate the role of neurotrophin signaling during airway epithelia repair. We studied the effects of 4 neurotrophins and 5 small molecule modulators when added to injured airway epithelia. The following criteria were used to evaluate neurotrophin influences on repair: (1) epithelia barrier integrity, (2) time to wound closure, (3) alterations in cell proliferation, and (4) cell population changes. We found that LM22-B10, a small molecule activator of TrkB/C, significantly impairs epithelia barrier integrity, dampens epithelia cell proliferation, and reduces the proportion of basal cells in a population. Despite these effects, wound-closure time remains unaltered by neurotrophin receptor agonism. Currently, our lab has several ongoing experiments working to verify the proposed LM22-B10 mechanism of action (TrkB/C and NGFR activation). While our data suggests TrkB/C stimulation alters the airway injury response, there remains a need to examine alternate synergistic activation of the Trk receptors, which may result in different cellular responses. Our lab has recently discovered that LM22-B10 similarly influences uninjured epithelia, however, future studies are needed to fully explore the roles of neurotrophins on the mature airway. In conclusion, our data suggests that neurotrophins may be important in regulating epithelial cell populations, especially during the injury response process. The literature surrounding neurotrophin function is narrowly focused on the nervous system, and our results indicate a need to expand the study of neurotrophin signaling to other body systems.

**Title**: Impact of Intraoperative Autologous Blood Transfusion on Elective Cardiac Surgery: A Retrospective Cohort Study

Student: Savantha Thenuwara
Mentor: Dr. Sudhakar Subramani, MD, FASE
Other Contributors: DR Satoshi Hanada, MD, FASE

**Introduction**: Allogenic transfusions are frequently used in cardiac surgeries, with over 50% of patients receiving transfusions. Even transfusion of 1 or 2 units of packed red blood cells has been associated with a dramatic increase of morbidity, mortality and costs in cardiac patients (1). Reducing the use of allogenic blood transfusions has been recommended for patients undergoing cardiac surgery whenever possible. Intraoperative autologous blood transfusion (IABT) is considered a blood conservation mechanism. This technique involves removing blood from the patient and storing in the operating room just before beginning of surgery. The blood is transfused back to the patient after surgery, or at the conclusion of intraoperative bleeding. This practice is effective at reducing postoperative bleeding, red blood cell transfusions and at reducing risk of postoperative pulmonary infections (2). Definitive reductions in allogenic red blood cell transfusion rates have been seen in some studies but not others that compared IABT to allogenic transfusions (3). This study aims to understand the impact of IABT in the setting of elective cardiac surgery at the University of Iowa Hospitals and Clinics. Specifically, it aims to compare IABT to allogenic blood transfusions during elective cardiac surgery and determine if a correlational relationship exists between autologous transfusion (IABT) and reduction in RBC transfusions as well as plasma, platelet and cryoprecipitate requirements within 48 hours of ICU admission.

**Methods**: The study included patients who underwent elective cardiac surgery at the University of Iowa in Iowa City, IA between July 1, 2017 and June 1, 2022. Those who received autologous blood transfusion were identified via a Q note in Epic (Epic Systems Corporation). Data was retrieved from Epic using Microsoft SQL Server Management Studio. Demographic data as well as pre-operative, intra-operative and post-operative data points were gathered. Propensity score matching was used to match the patients who received IABT with control subjects based on surgeon, type of surgery, surgery date as well as gender and age. A Fisher's exact test will be used for categorical data and a Wilcoxon signed-rank test will be used for continuous data.

**Results and Conclusion**: Within the 5-year span, 54 elective cardiac cases used autologous blood transfusion. 8 different surgeons carried out the 55 surgeries. 46 patients (85%) who received IABT were male and 8 (15%) were female. 52 of the 54 cases (96%) were conducted by the same anesthesiologist. Preliminary analyses are pending and will be presented at the Medical Student Research Conference.

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# Evaluating Provider Perspectives on Using Agenda Setting with Patients

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**Background** – Patient-provider communication plays a central role in influencing patient satisfaction and outcomes. To improve patient-provider communication at UIHC, all providers participate in a Provider Communication Program (PCP) which combines a 5-hour interactive skills workshop with postworkshop coaching to learn about best practices in communicating with patients. One communication strategy that is taught in the PCP, agenda setting, is an unfamiliar skill to many participants prior to the workshop. Agenda setting is an evidence-based skill that emphasizes eliciting all patient concerns early in the encounter and has been shown to support higher patient satisfaction and more efficient visits. However, informal reports of its underutilization and barriers to implementation call for more insight into providers' utilization of agenda setting during patient encounters.

**Objectives** – The aims of the study were to 1) evaluate providers' frequency of utilizing agenda setting before and after participating in the PCP, 2) to compare frequency of use based on clinical specialty and setting, and 3) to identify barriers that providers face when trying to incorporate agenda setting into patient encounters.

**Methods** - All providers (N=1273) who have participated in the PCP were surveyed through Qualtrics. The survey included questions about the providers' clinical specialties and settings, as well as their perceived utilization of agenda setting with patients before and after the PCP. Providers were asked to identify barriers that they face incorporating agenda setting in patient encounters. A total of 307 survey responses were received from 204 physicians, 90 advanced practice providers, and 23 other health professionals. Quantitative data was compiled into descriptive statistics while qualitative comments were summarized and categorized. All procedures were approved by the institution's IRB.

**Results** – Preliminary analysis showed an increase in agenda setting usage after PCP participation. Comparing providers in primary care, surgical specialties, and non-surgical specialties, those in primary care were more likely to utilize agenda setting. Responses revealed that common barriers to agenda setting included forgetting, disruptions, and time constraints rather than perceived value of using this skill. Qualitative analysis identified perceived barriers related to highly focused clinical specialties, inpatient clinical settings and patient or provider overall communication style.

**Conclusions** – This study provides an overview of the influence of the PCP on provider communication and a deeper insight into providers' utilization of agenda setting during patient encounters. With a better understanding of the barriers to agenda setting that providers face, PCP facilitators can tailor communication training for clinical specialties or settings. This allows participants from a larger variety of clinical backgrounds to benefit from communication training with the ultimate hope of promoting better patient care.

**Concordance of Steroid Response in Patients Treated for >1 Episode of Acute Alcoholic Hepatitis**

Student: Betty Tu
Mentor: Kyle E. Brown

**Background:**
Acute alcoholic hepatitis (AH) is a common, potentially life-threatening illness. Although corticosteroids (CS) are the only medical therapy of proven benefit in AH, up to 40% of patients with AH fail to respond to CS. The reason for steroid nonresponse in this condition is unknown. Host factors have been implicated in determining CS response, suggesting that responses to CS should be concordant in individuals who are treated on more than one occasion for AH.

**Objective:**
To assess steroid responsiveness of patients treated with CS for >1 episodes of AH and to determine whether there are clinical factors that are associated with discordant CS responses in this patient population.

**Methods:**
Patients seen at UIHC from January 1, 2016 and December 31, 2021 with a diagnosis of AH and documentation of treatment with CS for at least one episode of AH were identified (N = 122). Demographic, clinical, and biochemical data were collected from the electronic medical records. Of the 122 patients, 109 were treated for 1 episode (Group 1) and 13 were treated for >1 episodes (Group 2) of AH. Of Group 2, 12 patients were treated for 2 episodes of AH and 1 patient was treated for 3 episodes of AH. Steroid responses were determined based on the Lille scores (which incorporate change in total bilirubin since starting steroids as well as other laboratory parameters) calculated 4-7 days after initiation of CS.

**Results:**
Mean ages and the proportion of males/females were similar in the two groups. Of the 109 patients treated with CS for a single episode of AH during the study interval, 67 were steroid responders (61%). Of the 13 patients treated for multiple episodes of AH, 10 responded to CS in the first episode (77%), 9 in the second (69%) and the 1 patient treated for a third episode (100%). However, CS responsiveness was discordant in 5/13 (38%) patients treated for >1 episode of AH, with 3 patients who responded to CS in the first episode failing to respond to CS in a second episode; the converse was observed in 2 patients who were initially CS non-responders. Statistical analysis to identify clinical factors associated with CS response is pending.

**Conclusion:**
We found that more than 1/3 of patients who were treated for multiple episodes of AH had discordant responses to CS. Importantly, prior nonresponse to CS did not predict future nonresponse. Thus, a trial of CS is reasonable in patients with AH even if they have previously been a CS nonresponder. These data suggest that CS responsiveness in AH cannot be explained entirely by intrinsic host factors.

## ABSTRACT

### Investigating functional connectivity of cortical networks in presymptomatic children and adolescents at risk for Huntington's Disease

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**Background:** Huntington's disease (HD) is a progressive, lethal autosomal dominant disorder caused by a trinucleotide repeat mutation (CAG) in the huntingtin gene (HTT). HD's symptoms include motor abnormalities (involuntary movements or chorea), cognitive deficits, and behavioral changes. HD is autosomal dominant and easily tested with a blood sample so that people who are at risk (have a parent with HD) can get a gene test. This allows for the study of subjects who are preHD (have the gene expansion but do not yet have any symptoms) Studies have shown that adult preHD subjects exhibit abnormalities in brain structure, cognition, behavior, and motor function long before clinical diagnoses (up to 20 years). Given that the gene is normally involved in brain development, one theory suggests that some of the changes seen in the brain decades before disease onset may be due to abnormal development (rather than early degeneration). Functional Magnetic Resonance Imaging (MRI) is a method for evaluating the health of brain circuitry. For these reasons, we performed a novel study to investigate functional connectivity in different resting state networks and its impact on the clinical outcomes of preHD children and adolescents.

**Methods:** Participants' resting-state, functional MRI data as well as their neuropsychological test scores were provided from the Kids-HD study. Participants were grouped into gene expanded (GE) children (>35 CAG repeats) compared to gene non-expanded (GNE) children and population controls. In total, we evaluated seven cortical networks. The functional connectivity within each network was then quantified by taking the average connectivity across all regions of interest within the network. We utilized linear mixed effects regression models to compare the average connectivity of the defined networks across the two groups (GE vs. GNE). For any network that showed significant group differences, we did a within group analysis (GE only) to evaluate effect of network connectivity on cognitive and motor tasks.

**Results:** We report that GE individuals had decreased mean functional connectivity compared to the GNE individuals in the default mode, sensorimotor, and frontoparietal networks. Furthermore, in preHD subjects, decreased functional connectivity within the sensorimotor network was predictive of motor instability while decreased functional connectivity within the frontoparietal network was predictive of decreased executive scores.

**Conclusions:** This work is the first to assess functional connectivity within seven cortical networks in preHD children and adolescents. These children are far from motor onset, such that the degenerative processes that result in HD's symptoms have not yet begun. Therefore, the altered cortical network connectivity in presymptomatic children and adolescents may very well represent neurodevelopmental changes in the cortex early in life rather than neurodegeneration. This suggests that HD pathophysiology may be based in abnormal development, in conjunction to the current dogma based on degeneration.

# Basal Ganglia Network Alterations in Parkinson's Disease


## Authors

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## Disclosures

**H. Twedt:** None. **B. Yeager:** None. **J. Schultz:** None. **N. Narayanan:** None.


## Abstract

Changes to functional connectivity have been evidenced in Parkinson’s disease (PD), but the precise mechanisms and effects that lead to cognitive dysfunction have yet to be fully elucidated. We set out to understand the specific alterations to the brain’s functional architecture that result in cognitive impairment, with a focus on the basal ganglia network (BGN). The basal ganglia can control movements, but this group of structures also has important contributions to cognition. We hypothesize that there will be differences in the functional connectivity of the BGN in patients with PD when compared to healthy older adults. We also anticipate that this will relate to cognition. Neuroimaging data were used from the Parkinson’s Progression Marker Initiative (PPMI) dataset (N = 102). FMRI data were processed and analyzed using the CONN toolbox in MATLAB, where seed-to-voxel measures were computed for within-network connectivity. Using Pearson’s correlation coefficients as the measure of functional connectivity, we compared functional connectivity strength between three groups: healthy older adults (n = 20), patients with PD and normal cognition (PD-Norm; n = 67), and patients with PD and mild cognitive impairment (PD-MCI; n = 15). A linear mixed effects model was used to evaluate the effect of group on functional connectivity. Our first model showed a significant main effect of group on BGN functional connectivity, with a post-hoc comparison correcting for multiple comparisons revealing that PD-MCI patients have less functional connectivity within the BGN than older healthy adults. As an exploratory analysis, we evaluated inter-network functional connectivity between the BGN and frontoparietal network (FPN), given executive dysfunction is hallmark to PD and the FPN plays a major role in cognitive control. Consistent with our first model, we found that PD-MCI patients had less functional connectivity between the BGN-FPN than older healthy adults. These data provide evidence that functional connectivity is lowered within the BGN and between the BGN and FPN in PD patients who have cognitive impairment. Our findings suggest that impaired fronto-striatal networks contribute to cognitive impairments in PD.

Hidden Mechanisms of Coding Pathogenic Variants in *PTPRQ*

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**Introduction:**

Proper variant interpretation is at the heart of precision medicine. Misclassified variants result in misdiagnosis and can lead to improper clinical intervention. In diseases that show vast genetic, allelic, and phenotypic heterogeneity, such as hearing loss, proper variant interpretation is challenging. Each deafness-associated gene displays a unique genomic and mutational spectrum, the knowledge of which is a prerequisite to accurate variant interpretation for deafness. An additional layer of complexity is in the unrecognized and hidden mechanisms of action of some types of variants such as coding variants that impact RNA-splicing. In this study, we have investigated the mutational signature of the *PTPRQ* gene; one of the over 120 nonsyndromic deafness-associated genes. Interestingly, a vast majority of the variants linked to *PTPRQ*-related hearing loss are loss of function and are predicted to result in null alleles. Only a few missense mutations have been reported in *PTPRQ*. We predicted that some of the reported pathogenic missense variants in *PTPRQ* are benign, while the rest are disease-causing but exert their effect by altering RNA-splicing.

To investigate this hypothesis, variants of interest within *PTPRQ* were identified through a review of the literature and the internal Molecular Otolaryngology and Renal Research Laboratories (MORL) database. We then performed a minigene assay to assess these variants' effect on RNA splicing. Our results show that some pathogenic variants in *PTPRQ* exert their effect by altering normal splicing.

Our findings highlight the importance of gene-specific variant classification and the role some coding variants play on in altering normal RNA splicing. Identification of such variants is an important first step towards the development of appropriate treatments and therefore better outcomes for patients with *PTPRQ*-related deafness.

# Incidence of Success and Procedural Intervention after Mifepristone and Misoprostol for Miscarriage Management, Actual Clinical Use Study

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**Background:** Upon miscarriage diagnosis, women have three choices: expectant, medical, or procedural. Procedural intervention is predictable and 99% effective. However, many women often choose medical management to avoid procedures and to allow the pregnancy to pass at home. Optimizing the efficacy and safety of medication management of miscarriage is essential. Recent data has shown that a regimen containing mifepristone and misoprostol is the most effective medical management for early pregnancy loss (EPF). These data defined successful medical management as expulsion of a gestational sac. We suspect, however, that despite this "success," many patients still require procedural intervention due to other retained tissue. Therefore, we compared the need for procedural interventions after medical management versus surgical management.

**Methods:** All patients with EPL above the age of 18 from 1/1/2019 (when mifepristone/misoprostol regimen was started at UIHC) to 3/1/2022 were retrospectively identified and classified into those who received medical management (mifepristone and misoprostol) versus procedural management (uterine aspiration). Patients given the medications for reasons besides miscarriage management were excluded. Exclusion criteria for surgical management included initial procedures done to remove retained products of conception or complete/partial molar pregnancy. In addition, patients who chose expectant management first or had a pregnancy condition that required surgical management were excluded from both groups. Demographic information, successful expulsion of pregnancy, gestational information, the need for any additional procedural management, prescriptions, number of visits, phone calls, my-chart messages, ultrasounds, and complications were collected for both subject groups. Data analysis was done with OpenEpi 3.01. Continuous variables were described via mean and comparisons via t-test. Categorical data were described with proportions and analyzed using chi-square or Fisher exact test as appropriate.

**Results:** 96 eligible medication patients and 189 eligible surgical patients were identified. Patients were similar in age, insurance status, obesity, parity, and gestational age on ultrasound. 21.9% of the medically managed patients and 8% of surgically managed patients required a uterine aspiration or hysteroscopy to complete the miscarriage process (OR 3.23 (95% CI 1.58-6.64)). Among the medically managed patients, the reasons for an additional procedure were retained products (with bleeding 11.4%; without bleeding 4.2%) and incomplete expulsion of the gestational sac (5.2%). The additional procedure was rare among surgical patients and only for retained products (without bleeding 3.2%; with bleeding 4.8%). None of the surgical patients failed to remove the gestational sac. Urgent aspiration was required in 1 patient in each group (4.8% v 0.53%, OR 9.2 0.11-741.5), but this was not significant. Between procedural and medication patients, the indications for additional procedures were not significantly different (p=0.06). There were no differences in requirements for uterotonics, use of foley for tamponade, or post-treatment infection (analyzed via antibiotic prescriptions).

**Discussion:** Surgical management was more effective than medical management for miscarriage patients as it required to fewer additional procedures. Surgical management had less additional procedures due to retained products without bleeding or incomplete gestational sac expulsion. These data are consistent with the known precision of procedural management of miscarriage. Data demonstrating that 21% of medication management subjects required uterine aspiration allows providers to counsel patients about expectations and the efficacy of miscarriage management options.

## Abstract

**Title:** Indications and Effectiveness of Pre-Hospital Needle Thoracostomy

**Authors:** Gabriel E. Vazquez, BS; Hayden L. Smith, PhD; Jonathan R. Hurdelbrink, PhD; Cory C. Vaudt, DO; Beth A. Fuchsen, RN; Johnathon R. Calhoun, MD; Jeanette M. Capella, MD; Richard A. Sidwell, MD; Carlos A. Pelaez, MD, FACS

**Background:** Needle thoracostomy (NT), is a life-saving procedure used to treat tension pneumothorax. Indications for performing a NT include: 1) worsening respiratory distress or trouble manually ventilating; 2) unilateral missing or absent breath sounds; and 3) decompensated shock (i.e., SBP<90mmHg). There is concern that EMS providers may be performing the procedure without proper indication as studies have shown reduced/absent breath sounds may be a more common primary indication than hypotension. In addition, Iowa Methodist Medical Center (IMMC) has seen a steady increase in the number of NT's performed annually, starting in 2019.

**Objective:** To describe the indications, effectiveness, and adverse effects of prehospital needle thoracostomy for a Level 1 Trauma Center located in the Midwestern United States

**Methods:** A retrospective review of the IMMC Trauma Registry from January 2015 to May 2022 was conducted. The review included patients who received pre-hospital NT and a level 1 or 2 trauma activation prior to arrival at the center. Emergency Medical Services (EMS) and hospital records were reviewed to collect demographics and clinical course of patients receiving NT. Primary outcomes were: clinical characteristics of patients receiving needles; correct placement of needles; and complications of needles. Secondary outcomes were: pre-hospital improvement; need for chest tubes; hospital survival and length of stay.

**Results:** Sixty-three patients were included in the study, nine of whom were pronounced dead on arrival to the trauma center. Out of the 54 patients who survived to the center, four had documentation of all three criteria for needle decompression. The majority of patients receiving NT had reduced/absent breath sounds (86%), while hypotension (31%) and trouble breathing/ventilating (38%) were relatively under-represented in the patient sample. Thirty-eight patients survived in total, with a median length of stay of 6.0 days (interquartile range [IQR] 1.0, 22.0), with a median of 7.0 days (IQR: 3.0, 15.5) in the ICU. There were no statistically significant changes in documented pre-hospital vitals between before and after the patients received needles. Out of needles visible on computed tomography, 9 out of 21 reached the chest cavity. In all patients receiving imaging (n=54), there was evidence of 15 (28%) lung lacerations, 6 (11%) with an iatrogenic pneumothorax, and 3 (5%) near misses.

**Conclusions:** The presented study revealed that few patients fully satisfied criteria for needle decompression. There was little objective pre-hospital benefit to receiving needles, and evidence of iatrogenic injuries. Study data reinforced the importance of re-assessing the knowledge, attitudes, and practices surrounding the use of pre-hospital NT. Educational opportunities exist related to improving its utility.

**Title** The Prevalence of Pelvic Floor Disorders in Parous Ugandan Women

Ramya Vemulapalli
Mentors: Dr. Kimberly Kenne and Dr. Brooks Jackson
Collaborators: Dr. Michael Derrick Ngobi, Dr. Flavia Matovu Kiweewa, Julia Fleecs, JaNiese Jensen, Linder Wendt

**Background** Pelvic floor disorders (PFD) include urinary incontinence (UI), anal incontinence (AI), and pelvic organ prolapse (POP). Risk factors for PFD include parity, mode of delivery, and physical strain in daily life. Women in low- and mid-income countries (LMIC) often have higher parity and physical strain compared to those in high-income countries potentially putting them at higher risk for development of PFD. PFD negatively impact women's physical, emotional, and social wellbeing often without opportunity for treatment in LMIC. While previous studies have determined the prevalence of PFD in some LMIC, there is currently limited research in East African countries. The presence of PFD is generally determined by symptom assessment, standardized questionnaires, and a standardized physical exam. The short- form version of the Pelvic Floor Distress Inventory (PFDI-20) evaluates for the presence and degree of bother caused by PFD. The Pelvic Floor Impact Questionnaire (PFIQ-7) focusses on how the presence of PFD impacts a patient's life.
**Purpose of Study** The aim of this prospective cohort study is to determine the prevalence of PFD in parous Ugandan women as measured by symptom questions, standardized questionnaires, and physical exam.
**Methods** Women were recruited, enrolled, and consented from the Maternal Bone Health Study (MBHS), an ongoing study at the Makerere University-Johns Hopkins University Research Collaboration (MUJHU) in Kampala, Uganda. To assess the presence of PFD study personnel administered basic symptom questions, the PFDI-20, the PFIQ-7, and completed a standardized physical exam (Pelvic Organ Prolapse Quantification- POP-Q and Cough Stress Test- CST). Institutional Review Board approval was obtained through University of Iowa and MU-JHU. Variables are summarized using medians and inter-quartile ranges (IQR) for continuous variables, and with counts and percentages for categorical variables.
**Results** While study enrollment remains ongoing, 111 participants of the targeted 150 sample size have been enrolled as of August 22, 2022. The median age is 35 years old (IQR 32 – 38) and median BMI is 29 (IQR 24 – 33). The median parity and age at first delivery are 4 (IQR 3 – 5) and 19 (IQR 16 – 20), respectively. As measured by symptoms assessment 34 (31%) women had UI, and no participants reported AI or POP. Responses to the PFDI-20 (median 17, IQR 0 – 31) and PFIQ-7 (median 0, IQR 0 – 0) revealed minimal bother or impact on quality of life by PFD, respectively. As measured by the POP-Q, 60 (54%) participants had stage II prolapse or greater. 55 (50%) participants had a positive CST with a median bladder volume of 145 mL (IQR 81 – 235 mL).
**Conclusion** Pelvic floor disorders are prevalent in parous Ugandan women but appear to minimally bother women or impact their quality of life.

**Enhancing Culturally Responsive Foot Care for Patients with Diabetes:**
**An Assessment of Patient Experiences and a Proposed Educational Innovation**

Aneli Villa, BS and Martha L. Carvour MD, PhD

**Introduction:** Diabetes-related foot conditions (DFCs) result from reductions in blood flow, sensation, and wound healing in the legs and feet. DFCs are a significant cause of hospitalization, disability, and health inequity among patients with diabetes. Social and structural barriers to DFC care may include patients' perceived lack of control over their health or healthcare, the presence of other complicating physical or mental health conditions, lack of empathy and support from healthcare providers, limited access to educational information on foot care, and decisions by patients or providers to defer foot care or specialized medical attention (e.g., podiatry referral). Culturally responsive methods are needed to equitably equip patients and providers with information about DFC prevention, recognition, and care.

**Purpose:** A culturally responsive interventional tool called the Foot Book was piloted among patients and providers with the goal of enhancing patients' and providers' engagement in the foot care process.

**Methods:** People with diabetes from the University of Iowa Mobile Clinic, the University of Iowa Health Care (UIHC) Scott Blvd. Clinic, and 2 Storm Lake, Iowa community health fairs and healthcare providers from UIHC were eligible to participate in the study (IRB# 202205460). Recruitment was performed through active, in-person or passive, flyer-based methods for people with diabetes and email contact for healthcare providers. The Foot Book was revised, formatted, and translated into English and Spanish versions and then presented to participants during separate Zoom focus group sessions. During these sessions, participants completed pre-Foot Book and post-Foot Book surveys in Qualtrics that assessed their DFC knowledge and requested feedback about The Foot Book's content and design. Four weeks later, participants received a follow-up survey to reassess their DFC knowledge.

**Results:** A total of 5 participants (2 people with diabetes from Mobile Clinic and 3 healthcare providers from UIHC) participated in sessions, with a 100% response for all Qualtrics surveys (including the follow-up survey) to date. All participants were English-speaking. In the pre-Foot Book survey, both participants with diabetes agreed that they felt comfortable taking care of their feet, knew who to contact in case of a wound, were aware of the signs of a potential infection, and reported a good quality of life. In the pre-Foot Book survey, most healthcare providers agreed that they felt confident about their ability to educate patients about foot care, were well informed about DFCs, and knew what to do if one of their patients had a foot ulcer. However, most providers reported they had received minimal training on DFCs and wanted to learn more about wound care; none had DFC resources they could give to their patients. In the post-Foot Book survey, participants with diabetes recommended including more information about nutrition, while providers recommended including more advice about wound care. In terms of The Foot Book's design, participants with diabetes thought it should be delivered as a hard copy, whereas providers preferred both hard and digital copies. Participants with diabetes said they would use The Foot Book if given to them by a healthcare provider, and all healthcare providers agreed that they would distribute it to their patients. All participants agreed that a health professional should discuss information in the Foot Book with people with diabetes. Overall, most participants showed improvement in their knowledge and confidence in treating DFCs and found value in The Foot Book as an educational tool.

**Conclusion:** The Foot Book may be a useful tool for enhancing patients' and provider's engagement in the foot care process. The results of this pilot study will be used to further revise the Foot Book and implement a larger-scale interventional study in clinical and community settings. To continue to expand the inclusivity of the Foot Book during the design and implementation processes, additional focus group testing should be considered in-person and in dedicated Spanish focus groups, since the use of Zoom and the relatively short time available to recruit in language-diverse settings (Mobile Clinic and Storm Lake health fairs) may have limited participation during this pilot study.

**Impact of $^{123}$I-Ioflupane SPECT Results on Patient Diagnosis and Treatment**

Abby Walling; *Mentor: Michael Graham*

***Introduction:*** Parkinson's disease is a neurodegenerative disorder affecting about 1% of the global population over 60 years of age [1]. Despite its prevalence, the diagnosis of Parkinson's disease remains imperfect. Currently, Parkinson's disease can only be definitively diagnosed with post-mortem findings of intraneuronal inclusions of alpha-synuclein aggregates (Lewy bodies) in the pars compacta of the substantia nigra [2]. Thus, patients rely on clinical diagnosis based on four cardinal symptoms of bradykinesia, tremor, rigidity, and postural instability [3]. In recent years, clinicians have looked toward nuclear medicine to provide additional support in the diagnosis of Parkinson's disease. In 2011, the FDA approved the iodine-123 ioflupane dopamine transporter single-photon emission computed tomography (DaTscan) for use in the diagnosis of neurodegenerative diseases [3]. DaTscan images that show decreased nigrostriatal dopamine uptake can diagnose neurodegenerative parkinsonian syndromes, including Parkinson's disease, progressive supranuclear palsy, multiple system atrophy, Corticobasal degeneration, and dementia with Lewy body [4]. A normal DaTscan in a patient with parkinsonian symptoms can suggest an alternative diagnosis, such as essential tremor, anoxic or traumatic brain injury, intracranial mass, metabolic disorders, or hereditary disorders [4, 5]. Many research studies have aimed to determine the clinical utility of DaTscans and its impact on patient care. These studies have shown that 27-56% of DaTscans lead to a diagnostic change for the patient [6, 7]. The importance of DaTscans in clinical practice is further elucidated by studies that found a change in treatment for 44-66% of patients who received a scan [6, 8-10].

***Purpose:*** Although many studies have already demonstrated the importance of DaTscans in the diagnosis and management of Parkinson's disease, few studies have compared the impact of management for patients with a normal compared to an abnormal scan. This study was completed to compare diagnoses and medications of patients before and after DaTscans, and statistically analyze differences in diagnostic and medication changes between patients with normal and abnormal DaTscans. As the DaTscan passes its 10$^{th}$ year of FDA approval in the diagnosis of neurodegenerative diseases, it is important to determine the significance on patient care based on the study's result.

***Methods:*** This single-center retrospective study analyzed the charts of 100 patients who received a DaTscan and had an appointment with the University of Iowa Hospitals and Clinics Department of Neurology before and after the scan. The patient's DaTscan results were evaluated both visually by an experienced nuclear medicine physician and by the GE DAT QUANT program. The results were recorded, along with their top diagnosis (including Parkinson's disease, parkinsonism, tremor, Lewy body dementia, and others), any FDA-approved Parkinson's disease medication prescribed, and any medication changes during the neurology appointment before and the appointment after their DaTscan. Chi-squared and Fisher's exact tests were used to calculate the statistical difference between patient diagnoses, medication prescribed, and changes in medication treatment during the appointment before versus after the DaTscan. This same data was analyzed and stratified by the result of the DaTscan. Chi-squared and Fisher exact tests were used to calculate significant differences between patient diagnoses, diagnosis change, medication prescribed, and medication changes after a positive versus negative DaTscan. Alpha was set at 0.05. This study was IRB approved and no identifying patient information was reported.

***Results:*** A total of 100 patients were analyzed with DaTscans from August 2020 to March 2022. Overall, 38% of the DaTscans were read as abnormal. Before the DaTscan, 17% of patients were diagnosed with Parkinson's disease, 49% with parkinsonism, 20% with tremor, and 6% with Lewy body dementia; 39% were prescribed Carbidopa-Levodopa, 9% were prescribed a different medication, and 29% had a change in their prescription following the visit. Following a normal DaTscan, 3% of patients were diagnosed with Parkinson's disease, 33% with Parkinsonism, 18% with tremor, 3% with Lewy body dementia; 2% were prescribed with Carbidopa-Levodopa, 5% had a different medication prescription, 26% had a change in medication prescription, and 29% had a change in diagnosis during their visit. Following an abnormal DaTscan, 63% of patients were diagnosed with Parkinson's disease, 13% with Parkinsonism, 3% with tremors, 16% with Lewy body dementia; 24% were prescribed with Carbidopa-Levodopa, 29% had a different medication prescription, 50% had a change in medication prescription, and 45% had a change in diagnosis during their visit. There was no significant difference between any of the diagnoses, medications, or medication changes for patients before compared to after the DaTscan overall ($p > 0.05$). When stratified by the result of the DaTscan, there were significant differences between the patient diagnoses and medication prescriptions. Significantly more patients were diagnosed with Parkinson's disease, fewer were diagnosed with parkinsonism, fewer were diagnosed with tremors, more were given a new medication prescription, more were prescribed Carbidopa-Levodopa, and more had a change in medication following an abnormal compared to normal DaTscan result ($p < 0.05$).

***Conclusion:*** This study shows that overall, obtaining a DaTscan does not significantly impact patients' management. However, the patient's management is significantly different depending on the result of the DaTscan. An abnormal DaTscan was significantly more likely to lead to a diagnosis of Parkinson's disease, prescription of a new medication, prescription of Carbidopa-Levodopa, and change in any medication compared to a normal DaTscan. Alternatively, a normal DaTscan was significantly more likely to lead to a diagnosis of tremor. Therefore, the result of DaTscans have a statistically significant implication in patient diagnosis and treatment.

**Examining Long-Term Outcomes of High Tibial Osteotomies & Distal Femoral Osteotomies**
**Student: Michael Westphal**
**Mentor: Robert Westermann**

**Background**

Osteoarthritis of the medial knee compartment can be particularly difficult to treat, one non-arthroplasty option in patients with medial knee arthritis and varus alignment is the high tibial osteotomy (HTO), which is a surgical procedure designed to shift the load away from the degenerative medial knee articular cartilage. This study will solely focus on the medial wedge opening technique. A distal femoral osteotomy (DFO) aims to shift the load away from the lateral knee compartment in cases of valgus deformity. This study will focus on the lateral wedge opening technique for correction of valgus malformation.

Previous research has shown good long-term outcomes with survivorship rates defined as the percentage not converted to knee arthroplasty at given time.

**Methods**

First, potential subjects were identified via retrospective electronic medical review of patients who previously underwent a HTO or DFO procedure at UIHC prior to July 1, 2012. Subjects were contacted via EMR listed information to fill out the Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS Jr.) survey and list any additional surgeries undergone. The KOOS, JR. asks questions about stiffness, pain, and function/daily living, scored on a subjective scale from none to extreme, with a conversion to an interval score from 0 (no function) to 100 (perfect health). Survivorship rates were calculated based on surveys and record review.

**Results**

62 of 218 possible subjects have responded to the surveys thus far. The average interval KOOS Jr. score of these subjects was 71.7. 33 of the 62 subjects (53.2%) underwent an additional procedure, with the average being 1.02 additional procedures. 11 of the 62 subjects (17.7%) underwent a TKA prior to 10 years post-operatively, making the 10-year survivorship 82.3%. An additional 5 subjects underwent a TKA after the 10-year mark making the total survivorship 74.2%. The average time from HTO/DFO to TKA was 8.1 years.

**Discussion**

A systematic review published in 2020 by Ollivier et. al, examined the long-term survival rates for high tibial osteotomies at 5, 10, 15, and 20 years. The 10-year survival rates ranged from 64-97.6%, consistent with our 10-year survivorship being 80.4%. Unfortunately, due to the low number of DFO respondents, it is difficult to definitively state that these data points are significant, so we are unable to split the individual procedures at this time. Further recruitment of subjects is still ongoing.

**Title:** Identifying Visual Thresholds by Varying Stimulus Size

**Student Author:** Anushi Wijayagunaratne, M2

**Faculty Mentors:** Michael Wall, MD, Department of Neuro-ophthalmology; Edward Linton, MD, Department of Neuro-ophthalmology

**Collaborators:** Iván Marín-Franch, PhD, Computational Optometry

**Background:** Perimetry, or formal visual field testing, is used in clinical medicine to detect areas of visual loss caused by damage to visual pathways. This allows clinicians to localize pathology and to monitor the progression and treatment response of disease over time. Standard automated perimetry (SAP) finds thresholds of the central visual field by presenting a series of light stimuli between 0 dB (bright) to 40 dB (dim) luminance against a uniform background. Unfortunately, retest variability worsens with visual field damage, and it has been recently shown that SAP is unable to monitor visual function worse than ~20dB. Consequences of this finding are that often the most clinically important areas of the visual field (areas of lower visual sensitivity) are the regions where evaluation of visual sensitivity changes is most problematic. A type of perimetry that is not as plagued by increasing variability with worsening sensitivity could substantially help clinicians and their patients with optic nerve damage make more confident clinical decisions. Previous studies have found that stimulus size-modulation strategies, rather than luminance variation, perform with lower retest variability as measured by the standard deviation of the visual psychometric function known as "frequency of seeing (FOS) curve," which did not increase with worsening disease. If it is determined that obtaining visual thresholds by varying stimulus size rather than stimulus contrast is a more reproducible method of perimetry, this finding holds the potential of changing the way clinical perimetry is done and increasing access to care by allowing inexpensive virtual reality perimeters, which run on a smartphone, to be accessible for at-home testing.

**Purpose:** To validate the Iowa Head Mounted Display perimeter (HMD) by comparing stimulus contrast-variability frequency of seeing (FOS) curves of this perimeter with a standard automated perimetry device, the Octopus 900 (O900), and to test the hypothesis that stimulus size-modulation testing with the HMD yields lower variability than the current clinical standard of fixed size contrast-modulation in areas of reduced retinal sensitivity.

**Methods:** Participants included 15 ocular healthy subjects and 1 glaucoma patient. Each participant underwent testing on the Octopus 900 varying luminance at a stimulus diameter of 0.43 degrees (Goldmann size III). A second test was done using the HMD perimeter that varied luminance with the same fixed stimulus size. In addition, a third test was done with the HMD perimeter that *varied stimulus size* with a fixed stimulus luminance of 1 cd/m$^2$. Frequency-of-seeing data were generated for each of these three methods using the method of continuous stimuli (MOCS) at three locations of increasing eccentricity in a single eye of each participant, with a total of 30 presentations at each stimulus interval. Test locations of increasing eccentricity showed reductions in retinal sensitivities. FOS curves were modeled by logistic regression with guess and lapse rate as free parameters. The contrast- or size-threshold was defined for each subject, condition, and test location as the log(contrast) or log(area) respectively at threshold (50% probability of being seen). The slope of the psychometric function at threshold, and the goodness of fit of the function to the data were calculated for each FOS curve, as a steep slope and good fit represent excellent reproducibility. Threshold, slope at threshold, and goodness of fit were compared between conditions in each subject group, as well as by pointwise analysis. The effect of eccentricity on threshold, FOS slope, and goodness of fit when varying luminance on the O900, luminance on the HMD, and size on the HMD was also evaluated.

**Results:** There was no significant difference found between the estimated contrast threshold measured between the O900 and HMD for the fixed size condition. All three methods showed the expected decrease in visual sensitivity at more peripheral locations ($p<0.01$). Pointwise threshold data show good agreement between HMD and SAP on the Octopus 900 in estimation of contrast thresholds, along with a strong linear correlation between luminance and size thresholds with the HMD. HMD contrast modulation showed no significant difference in slope of FOS when compared to the O900 but showed better goodness of fit measures. HMD size modulation showed shallower slopes on a scale of log(area) when compared to the O900, but no significant difference in goodness of fit measure.

**Conclusion:** The HMD was able to measure contrast thresholds with good agreement to the O900, showing that the two devices are behaving similarly. Retest variability as estimated by FOS curve goodness of fit was not increased by varying stimulus size at 1 cd/m$^2$ at any of the three locations compared to the gold standard luminance modulation with the Octopus 900. Our results help validate the Iowa HMD perimeter. In addition, the HMD perimeter shows much promise as a size modulation perimeter. Further testing on glaucoma patients is needed to further validate this perimeter.

**Comparison of hyperangulated versus standard geometry video laryngoscopy in a simulated helicopter emergency medical service setting: A randomized crossover trial**

Clara J Wilhelm, BS; Layden L. Smith, PhD; Jonathan R. Hurdelbrink, PhD; Cory C. Vaudt, DO; Chad M. Nelson, RN; Gabe E. Vasquez, BS; Brian P. Jennett, MD*

**Background:** Video laryngoscopy (VL) has become a common tool for endotracheal intubations in the prehospital setting. It has been shown useful in patients with difficult airways. The comparison of hyperangulated video laryngoscopy (HAVL) and standard geometry video laryngoscopy (SGVL) techniques in the prehospital setting remains minimally studied.

**Objective:** To investigate whether there are differences between HAVL and SGVL in a Helicopter Emergency Medical Services (HEMS) setting in non-physician providers.

**Methods:** A three-center, randomized crossover trial was conducted with HEMS nurses and paramedics. Participants were randomized to perform 5 intubations in a grounded helicopter on an airway manikin with HAVL or SGVL first followed by 5 intubations with the subsequent technique. Outcomes included time to intubation, first-pass success rates, Cormack Lehane scores, and subjective preferences based on survey response data.

**Results:** The study sample included 30 participants and failed to reveal a difference between mean time to intubation for HAVL and SGVL (-1.4; 95% CI: -3.9, 1.1 seconds). HAVL and SGVL were identical in terms of first pass success and Cormack-Lehane scores for HAVL revealed 91% of attempts having grade 1 views versus 81% for SGVL (OR: 2.5; 95% CI: 0.83, 7.5). Survey data demonstrated participants perceived SGVL as requiring more force to achieve a proper glottic view (27/30) and HAVL as having better glottic views (21/30), increased confidence in passing an endotracheal tube (17/30), better first-pass success (21/30), and being preferred overall (21/30).

**Conclusion:** Overall, there was no differences found between HAVL and SGVL, although providers did seem to subjectively prefer HAVL. The main limitation of the study was its simulation design, which can only replicate a rapidly deteriorating HEMS patient to a certain extent. Although the study demonstrated both techniques as suitable for intubation, it is up to the provider's discretion to select a technique based on preferences and patient's unique situation and anatomy.

**The Impact of Inter-hospital Transfer on Elements of Sepsis Care Prior to Transfer**

**Student: Cole Wymore, M2**
**Mentor: Nicholas Mohr, Emergency Medicine**

Background: Sepsis patients in low-volume emergency departments (EDs) have a 38% higher mortality compared to their urban counterparts. Early aggressive care has shown to improve mortality, but many transferred sepsis patients in rural areas have low adherence with national resuscitation guidelines. While appropriate time-sensitive care can be delivered before and during the interhospital transfer process, the impact that interhospital transfer has on early sepsis care amongst rural patients is still not completely understood. The objective of this study was to assess to what extent interhospital transfer delays the time to completion of the Surviving Sepsis Campaign 3-hour bundle among rural sepsis patients.

Methods: We conducted a multi-center (N=23) retrospective cohort study among sepsis patients in a midwestern rural ED-based telemedicine (tele-ED) network from August 2016 to June 2019. All adults (age ≥ 18 year) seen in a participating rural EDs who had sepsis, defined as infection and organ failure in the ED were included. Any patients transferred to a hospital outside the network were excluded for missing inpatient data. Data were collected using manual chart abstraction, with the primary exposure of transfer status and primary outcome of time to completion of 3-hour bundle. We used generalized estimating equations and a random intercept of hospital to measure the adjusted association between transfer and bundle adherence. Secondary outcomes included adherence with each component of the sepsis bundle and mortality.

Results: A total of 1,191 patients were include with 359 (30%) undergoing interhospital transfer. Bundle adherence (3-hour) was observed in 152 (12.5%) patients. Bundle adherence was similar among patients who were transferred compared to patients who were not (12.0% transferred vs. 13.1%, difference 1.1%, 95% CI [-3.0] – 5.2). The time to completion of the 3-hour bundle was also similar (103.5 vs 111.0 min, difference 7.5 min, 95% CI [-5.2] – 19.2). ED length-of-stay was 7.0 hours (95% CI 0.20–0.38) longer for those who were transferred than those who were admitted locally.

Conclusion: Rural sepsis patients undergoing interhospital transfer have similar adherence and time to completion of the 3-hour sepsis bundle as those who were admitted locally.

**Perilunate Injury Outcomes, Treatment, and Diagnosis rate - A Retrospective Study**

Lydia Yang, M2, Jill Corlette, Lindsey Caldwell, MD

**Background**: Perilunate injuries are a pattern of injury to the wrist that result the lunate dissociating from the rest of the carpal bones. They have been described as rare, high-energy injuries that are missed on initial presentation in up to 25% of cases. Previous studies report median nerve symptoms in as many as 45% of cases and have reported that cases in which the lunate is displaced from its fossa and rotated >90 degrees (Herzberg IIB) are irreducible in a closed manner. The data sources for these papers were largely collected >20 years ago and have not been updated in the current practice environment.

**Specific Aims of Study:**

1. Determine if patients treated at UIHC have higher reducibility of stage IIB dislocations, lower levels of missed diagnosis, and lower incidence of median nerve injury than previous studies
2. Add a significant number of recently treated perilunate injuries to the sparse and dated data currently available

**Hypothesis**: We hypothesize that the current rate of missed diagnosis and rate of median nerve injury requiring operative intervention is lower than previously reported, and the rate of successful closed reduction is higher than previously reported.

**Methods**: A retrospective review of patients with perilunate injuries seen at University of Iowa Hospitals and Clinics treated between January 1, 2008, to April 15, 2022 was performed. Demographic information, mechanism of injury, concurrent injuries, comorbidities including Charleston Comorbidity Index, Herzberg classification, time from injury to diagnosis, operative and non-operative treatment, subsequent surgeries, presence or absence of median nerve injury, length of follow up and most recent follow up were collected and reviewed. Exclusion criteria included all patients without a perilunate injury.

**Results**: Of 53 patients with perilunate injuries, 47 (88%) were male with an average age of 34 years. High energy incidents accounted for 34 (64.15%) cases, and 16 (30.19%) cases were part of polytraumas No patient presenting primarily to our institution had a missed or late diagnosis. Four patients presented to our institution late after being missed clinically or radiographically at outside institutions and 3 perilunates presented in a delayed fashion after being detected at an outside institution.

The majority were classified as Herzberg I (35, 66%) with 11 (20.8%) Herzberg IIA and 7 (13.2%) Herzberg IIB. Overall, 42 (79.2%) of patients underwent attempted closed reduction, 40 (95.2%) of which were successful. Only 2 (5%) of attempted closed reductions were unsuccessful. In the Herzberg IIB group 100% of the closed reductions attempted were successful. Ultimately, 94% of patients were surgically treated through an open reduction of the perilunate. In addition, to the open reduction, 44 (83%) patients had ligamentous pinning, 23 (43%) underwent ligamentous repair, and 16 (30) had a carpal tunnel release. Patients with median nerve symptoms decreased from 29 (54.72%) at presentation to 15 (28.3%) after non-operative treatment with a closed reduction, to 12 (22.64%) post-surgical intervention. Average duration of care was 207 days (6.8 months).

**Conclusion:** Among patients presenting primarily to our institution there were no missed or delayed diagnoses. Rate of median nerve symptoms were similar to historic studies, the majority of which resolved with closed reduction and subsequent surgical management. Of note, the rate of successful closed reduction of perilunates at our institution was 95.2% overall and 100% for Herzberg IIB, suggesting that these are more amenable to closed reduction than previously reported.

**Keywords: perilunate, median nerve injury, lunate dislocation, acute carpal tunnel syndrome**

# Surgical Site Infection (SSI) Rates in Patients with Acute Bowel Perforation: Is Rapid Source Control Laparotomy (RSCL) better than Laparotomy with Primary Fascial Closure (LPFC)?

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**Background**. Surgical site infections (SSIs) are the most common hospital-acquired infections in the perioperative period. Depending on the anatomic level of the infection, SSIs are divided into: superficial incisional, deep incisional, and organ/space infections. The consequences of SSIs include prolonged hospital stay, and higher morbidity and mortality rates. Studies have shown that SSI rate increases as wounds become more contaminated, classified as clean, clean/contaminated, contaminated, and dirty/infected. Rapid source control laparotomy (RSCL) is a staged surgical operation that leaves the abdomen open after initial contamination control. We hypothesized that, in patients undergoing emergent small bowel and/or colon surgery, RSCL would lower SSI rates because it allows for multiple abdominal irrigations as compared to laparotomy with primary fascial closure (LPFC).

**Objectives**. The main objective of this study was to assess whether RSCL can lower SSIs development. In addition, the factors that significantly impact SSI development were also investigated.

**Methods**. Patients undergoing emergent small bowel and/or colon surgery from 2006 to 2021 at our institution and entered in the National Surgical Quality Improvement Program (NSQIP) database were included in this study. Demographics, wound classification, laparotomy incisional closure type (RSCL, LPFC, and LPFC and skin closure (LPFSC)), comorbidities, and SSI were retrospectively collected. Both univariate analysis and binary logistic stepwise (backward) regression were performed to identify significant factors associated with each type of SSI. $P < 0.05$ was considered significant.

**Results**. A total of 906 patients were included, 214 were managed with RSCL on the first surgery, 175 underwent primary fascia closure only, and LPFSC for 517 subjects. Among the RSCL patients, 0.9%, 7.0%, 15.9%, and 76.2% presented with a clean, clean/contaminated, contaminated, and dirty/infected wound, respectively. For the LPFC patients, 1.1%, 4.6%, 15.4%, and 78.9% presented with a clean, clean/contaminated, contaminated, and dirty/infected wound, respectively. Finally, 8.9%, 22.8%, 22.6%, and 45.6% of the LPFSC patients presented with a clean, clean/contaminated, contaminated, and dirty/infected wound, respectively. Overall, surgical management differed significantly between the wound classification groups ($p < 0.001$). Patients in the clean and clean/contaminated groups were more likely to have LPFSC on the first surgery (92% vs. 83.7% vs. 65.7% vs. 43.9%), while LPFC (4% vs. 5.7% vs. 15.2% vs. 25.7%) and RSCL (4% vs. 10.6% vs. 19.1% vs. 30.4%) were more likely to be performed when the wounds were classified as contaminated or dirty/infected. A total of 66 patients developed superficial SSI (4.2% RSCL vs. 1.7% LPFC vs. 10.4% LPFSC, $p < 0.001$), six patients developed deep incisional SSI (0.5% RSCL vs. 0% LPFC vs. 1.0% LPFSC, $p = 0.364$), and 97 patients developed organ/space SSI (17.3% RSCL vs. 9.7% LPFC vs. 8.3% LPFSC, $p = 0.002$). Multivariate analysis revealed that BMI, preoperative acute renal failure, wound classification, preoperative superficial SSI, and incisional closure type were significantly associated with superficial SSI development. Compared to LPFSC, RSCL and LPFC were associated with a lower risk of superficial SSI (OR = 0.377 [0.165, 0.858], $p = 0.012$ and OR = 0.121 [0.028, 0.516], $p = 0.003$, respectively). For organ/space SSI, the significant factors included age, gender, ASA score, wound classification and preoperative organ/space SSI, but not incisional closure type. Compared to presenting with a clean wound, presenting with clean/contaminated or dirty/infected wounds was associated with a lower risk of organ/space SSI (OR = 0.170 [0.029-0.985], $p = 0.048$ and OR = 0.225 [0.065-0.780], $p = 0.019$, respectively). The RSCL patients were then analyzed by the incisional closure type of their last operation with no significant difference observed in SSI rates among these patient groups.

**Conclusion**. As subjects presented with a contaminated wound, compared to LPFSC, both RSCL and LPFC surgical management significantly lowered superficial SSI rate. Presenting with dirty/infected wounds was associated with a lower risk of organ/space SSI. Finally, for patients who underwent RSCL on the first surgery, the incisional closure type of their last operation did not significantly affect the SSI development. One limitation of the results is that the data analysis was underpowered due to limited case numbers. Additional studies are underway using the National Surgical Quality Improvement Program (NSQIP) national data.

# The Functional Consequences of Radiation Treatment in Soft Tissue Sarcoma of the Extremity

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**Background**

Functional outcomes of soft tissue sarcoma (STS) treatment are difficult to determine due to the rarity and heterogeneity of the disease. To date, the functional outcomes of STS patients who received radiation treatment versus those who did not are yet to be fully investigated. Balancing the amount of tissue that needs to be resected in order to minimize local recurrence, while preserving as much tissue as possible to maintain function, is an important and clinically relevant dilemma. Radiation treatment allows the resection to be closer to the tumor itself, yet has some functional costs of its own. Complications of radiation that may impede function include stiffness, pain, swelling, secondary malignancy, as well as problems with wound healing.

This retrospective cohort study includes University of Iowa Health Center (UIHC) patients who were treated for STS of the extremities with and without radiation treatment. As the functional impact of radiation on patients with STS of the extremity has not yet been quantified, the goal of this project was to determine its impact on patients' functional outcomes. An additional aim of the project is to analyze the temporal trends of recovery.

**Hypothesis/Aims**

We predict that radiation treatment will negatively impact the functional outcomes of patients with STS of the extremities. The specific aim of the study is to see whether or not there is a significant difference in the functional outcome scores of STS patients who were treated with radiation compared to those who did not undergo radiation treatment.

**Method**

Our retrospective chart review included patients treated between September 2010 to June 2022, identifying all patients with a non-metastatic intermediate- or high-grade STS of the extremities who were treated at UIHC. This data was primarily sourced from Epic. Within this date range, the cohort included a total of 198 patients that were then further screened to determine whether they met inclusion and exclusion criteria. The inclusion criteria for patients were primary STS that were >5 cm at time of diagnosis, deep to the muscle fascia, treated with limb sparing surgical resection for curative intent, and had a minimum of two recorded functional outcome scores. Exclusion criteria consisted of incomplete medical records, superficial lesions, tumors <5 cm at time of diagnosis, prior radiotherapy to the location, and concurrent unrelated malignancy. We did not include functional outcome scores for patients after local recurrence, metastasis, or amputation. Once evaluated for inclusion and exclusion criteria, 119 patients remained.

These patients were then sorted based on those who received radiation treatment versus those who did not. These groups were then further subcategorized by tumor type (neural sarcoma, synovial sarcoma, leiomyosarcoma, rhabdomyosarcoma, liposarcoma, fibrous sarcoma, vascular sarcoma, undifferentiated sarcoma, and other (including sarcomas of uncertain differentiation)), tumor size at time of resection, timing and dose of radiation, systemic treatment, region (lower extremity, upper extremity), location (hip/pelvis, thigh to and including the knee (no hip), below the knee, shoulder/axilla, arm to and including the elbow, below the elbow), return to operating room/wound healing complications, sex, and age. Next, functional outcomes were assessed using one or more of the following: Musculoskeletal Tumor Society (MSTS) Score, Toronto Extremity Salvage Score (TESS), or Patient-Reported Outcomes Measurement Information System (PROMIS) Global-10. These scores were then classified as being pre-operative (baseline), 6 months post-operative (scores recorded between 4 and 8 months post-operative), one year post-operative (between 8 and 15 months), or over two years post-operative (greater than 15 months).

**Results**

The average age at the time of surgery for our cohort was 61.4 years, with 67 males, 51 females, and 1 transgender female. The three most common histologic diagnoses were undifferentiated sarcoma (50), fibrous sarcoma (17), and liposarcoma (16). 71 patients received pre-op radiation, 26 received post-op radiation, and 22 patients received no radiation. Ultimately, there were 54 males, 42 females, and 1 transgender female who received radiation, while 13 males and 9 females received no radiation. The top histologic diagnosis for those who received radiation was undifferentiated sarcoma (46) and for those who did not receive radiation, it was fibrous sarcoma (6). The average age of patients receiving radiation treatment was 60.4, and 65.9 for those who did not.

The statistical analysis is currently being performed and includes a univariate analysis to compare those who received radiation versus those who did not, as well as to compare different locations and tumor sizes. It is our expectation that the results will contribute to greater understanding regarding the impact of radiation therapy on patients with STS of the extremities.

**Conclusion/Discussion**

This study performed a novel comparison, as the consequences of radiation therapy have not yet been quantified for patients with STS of the extremities. The outcomes of this study will be used by clinicians to develop optimal treatment plans and to better inform and counsel their patients by having a more accurate understanding of the risks and benefits of radiation therapy.

# Efferent projections of *Nps* parabrachial neurons in mice

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Neuropeptide S (NPS) neurons form two clusters at the midbrain-hindbrain junction. A dense, rostral cluster in the lateral parabrachial nucleus extends to the nucleus of the lateral lemniscus. A smaller, caudal cluster borders the locus coeruleus. The output connections of the parabrachial region are known, but we lack specific information about the projection patterns of NPS neurons. Here, we used Cre-dependent anterograde tracing and whole-brain analysis to map their efferent projections. While most parabrachial axons reach the forebrain via a ventral pathway or the central tegmental tract, NPS axons traveled along periventricular and ventral pathways. None followed the central tegmental tract. Along the periventricular pathway, NPS neurons densely targeted the periventricular nucleus of the thalamus and an uncharted, inter-collicular region. Along the ventral pathway, NPS neurons heavily targeted the subparaventricular zone, dorsomedial hypothalamic nucleus, subparafasciular thalamic nucleus, and ventral bed nucleus of the stria terminalis, along with sparse labeling in several other regions. Prominent terminal fields in the paraventricular thalamic nucleus, subparaventricular zone, and dorsomedial hypothalamic nucleus suggest that NPS neurons modulate stress responses and circadian rhythm. This information provides a framework for studying the functional effects of NPS neurons.