ALPHA ØMEGA
ALPHA

47TH ANNUAL SCIENTIFIC
RESEARCH SYMPOSIUM

Friday, August 5, 2016
Great hall
The Mary Duke Biddle Trent Semans Center for Health Education
Άξιον ωφελείν τους αλγούντας

"Be worthy to serve the suffering"
A. Eugene Washington, MD
Chancellor for Health Affairs, Duke University
President and CEO, Duke University Health System

“Don’t Throw Away Your Shot: How You Seize This Golden Moment”

Friday, August 5, 2016
The Mary Duke Biddle Trent Semans Center for Health Education
Great Hall

7:30 - 8:00 AM Platform Presentation Setup
Breakfast – Served in the Great Hall Lobby, level 0

8:00 - 8:30 AM Keynote Address: Eugene Washington, MD

8:40 - 11:00 AM Platform Presentations

11:00 - 12:45 PM Poster Presentations

12:45 - 1:30 PM Pick up lunch – Learning Hall, level 2

RETURN TO THE GREAT HALL FOR 1:30 PM PRESENTATIONS

1:30 – 2:15PM Dr. Ed Buckley and Dr. Colleen Grochowski: Curriculum Updates

2:15 - 2:45PM Colin O’Leary, Davison Council President

2:45 – 3:00 PM Presentation of Awards

3:00 PM Adjourn
The Duke AΩA Chapter would like to thank the following for their participation in today’s Symposium:

Platform Judges

A. Eugene Washington, M.D.
Chancellor for Health Affairs, Duke University
President and CEO, Duke University Health System

Edward Buckley, M.D.
Professor of Ophthalmology; James Pitzer Gills, III, M.D. and Joy Gills Professor of Ophthalmology in the School of Medicine; Professor in Pediatrics;
Vice Dean for Education; Chair, Department of Ophthalmology

Victor J. Nadler, Ph.D.
Professor Emeritus of Pharmacology & Cancer Biology,
Professor of Neurobiology

Daniel Laskowitz, M.D., M.H.S.
Professor and Vice Chair of Neurology; Professor of Anesthesiology & Neurobiology; Director, Neurovascular Laboratories

Philip Rosoff, M.D., M.A.
Professor of Pediatrics (Hematology-Oncology), Professor of Medicine;
Director of Clinical Ethics, Duke University Hospital

Poster Judges

Abraham, Dennis, M.D., Assistant Professor of Medicine, Director, Duke Cardiovascular Physiology Core, Division of Cardiology
Alspaugh, Andrew, M.D., Professor of Medicine. Professor in Molecular Genetics and Microbiology
Andolsek, Kathryn, M.D., MPH, Associate Director, Graduate Medical Education; Community and Family Medicine
Badea, Alexandra, Ph.D., Assistant Professor of Radiology, Center for InVivo Microscopy
Batinic-Haberle, Ines, Ph.D., Professor of Radiation Oncology
Brennan, Todd, M.D., MS, Assistant Professor of Surgery- Abdominal Transplant
Challa, Pratap, M.D., Associate Professor of Ophthalmology
Chiba-Falek, Ornit, Ph.D., Assistant Professor of Neurology, Department of Neurology, Bryan Alzheimer's Disease Research Center and Duke Institute for Genome Sciences & Policy
Chitneni, Satish, Ph.D., Assistant Professor of Radiology, Member of Duke Cancer Institute
Chu, Vivian, M.D., MHS, Associate Professor of Medicine-Infectious Diseases
Crowley, Anna Lisa, M.D., Associate Professor of Medicine-Cardiology
Crowley, Stephen, M.D., Associate Professor of Medicine-Nephrology
Daubert, James, M.D., Professor of Cardiology- General Electrophysiology
Driehuys, Bastiaan, Ph.D., Professor of Radiology, Professor of Physics
Dupre, Matthew, Ph.D., Associate Professor in Community and Family Medicine
Fecci, Peter, M.D., Ph.D., Assistant Professor of Neurosurgery, Assistant Professor in Pathology
Freedman, Neil, M.D., Associate Professor of Medicine, Assistant Professor in Cell Biology
Frush, Donald, M.D., John Strohbehn Professor of Radiology
Gottschalk, William Kirby, Ph.D., Assistant Professor of Neurology
Grotegut, Chad, M.D., Associate Professor of Obstetrics and Gynecology
Gunn, Michael Dee, M.D., Professor of Medicine - Cardiology
Gurley, Susan, M.D., Ph.D., Associate Professor of Medicine - Nephrology
Hobson-Webb, Lisa, M.D., Associate Professor of Neurology
Holley, Christopher, M.D., Ph.D., Assistant Professor of Medicine - Cardiology
Kelley, Michael, M.D., Professor of Medicine, Member of Duke Cancer Institute
Kraus, William, M.D., Professor of Medicine – Cardiology, Professor in the School of Nursing,
Professor of Biomedical Engineering, Member of Duke Molecular Physiology Institute, Member of Duke Cancer Institute
Kuo, Anthony, M.D., Assistant Professor of Ophthalmology
Limkakeng, Alexander, M.D., M.H.S., Associate Professor of Surgery
Matsunami, Hiroaki, Ph.D., Professor of Molecular Genetics and Microbiology, Professor of Neurobiology, Member of Duke Cancer Institute, Faculty Network Member of the Duke Institute for Brain Sciences
McNulty, Amy, Ph.D., Assistant Professor of Orthopaedic Surgery, Assistant Professor of Pathology
McPeek Hinz, Eugenia, M.D., M.S., Associate CMIO, Duke University Health System
Michener, James Lloyd, M.D., DTMI - Duke Center for Community Research (DCCR); Professor of Community and Family Medicine; Clinical Professor, School of Nursing; Chair, Department of Community and Family Medicine
Moon, Richard, M.D., Professor of Anesthesiology, Professor of Medicine – Pulmonary, Allergy and Critical Care Medicine, Medical Directory, Hyperbaric Center
Nadler, Victor J., Ph.D., Professor of Pharmacology & Cancer Biology, Department of Neurobiology
Nelson, Rendon, M.D., Reed and Martha Rice Professor of Radiology, Professor of Radiology, Professor in Department of Mechanical Engineering and Materials Science, Member of the Duke Cancer Institute
Parker, William, Ph.D., Associate Professor of Surgery
Permar, Sallie, M.D., Ph.D., Assistant Professor of Pediatrics- Infectious Diseases, Associate Professor in Immunology, Associate Professor in Molecular Genetics and Microbiology, Member of Duke Human Vaccine Institute, Affiliate, Duke Global Health Institute
Price, Thomas, M.D., Associate Professor of Obstetrics and Gynecology
Rajagopal, Sudarshan, M.D., Assistant Professor of Medicine – Cardiology, Assistant Research Professor in Biochemistry
Rao, P. Vasantha, Ph.D., Professor Ophthalmology, Professor in Pharmacology and Cancer Biology
Reiman, Robert, M.D. Associate Professor of Radiology
Sampson, John, M.D., Ph.D., M.H.S., M.B.A., Robert H., M.D. and Gloria Wilkins Professor of Neurosurgery, Professor of Neurosurgery, Professor of Immunology, Professor of Radiation Oncology, Professor of Pathology, Professor of Biomedical Engineering, and Member of the Duke Cancer Institute
Shah, Svati, M.D., Associate Professor of Medicine – Cardiology, Member in the Duke Clinical Research Institute, Member of the Duke Molecular Physiology Institute
Shapiro, Mark, M.D., Associate Professor of Surgery
Shenoy, Sudha, Ph.D., Associate Professor of Medicine – Cardiology, Associate Professor in Cell Biology, Member of the Duke Cancer Institute
Silberberg, Mina, Ph.D., Associate Professor in Community and Family Medicine
Sosa, Julie, M.D., Professor of Surgery, Professor of Medicine – Medical Oncology, Member of the Duke Clinical Research Institute, Member of the Duke Cancer Institute
Sparks, Matthew, M.D., Assistant Professor of Medicine - Nephrology
Stiber, Jonathan, M.D., Assistant Professor of Medicine - Cardiology
Sunday, Mary, M.D., Ph.D., Professor of Pathology
Swamy, Geeta, M.D., Associate Professor of Obstetrics and Gynecology, Member of the Duke Human Vaccine Institute
Thielman, Nathan, M.D., Professor of Medicine, Research Professor of Global Health, Professor of Pathology
Tomaras, Georgia, Ph.D., Professor in Surgery, Professor in Immunology, Professor in Molecular Genetics and Microbiology, Member of the Duke Human Vaccine Institute, Affiliate of Duke Global Health Institute
Tornai, Martin, Ph.D., Associate Professor of Radiology, Member of Duke Cancer Institute

**Special Thanks**
Mr. E. Arthur Palumbo, a 1949 Duke University graduate, established The Palumbo Family Medical Scholarship which provides a full-tuition scholarship for the fourth year of medical school and will be awarded today. Mr. Palumbo is a great friend of Duke Medicine who has also provided major funding to Duke Children’s Hospital, and who also established The Leonard Palumbo, Jr., MD Faculty Achievement Award in memory of his brother – a Duke University School of Medicine alumnus (MD 1944) and former Duke Obstetrics and Gynecology faculty member. The award is given annually to one or more Duke School of Medicine faculty members who best exemplify the qualities of compassionate patient care and dedication to teaching and mentoring young physicians that his late brother embodied.
PLATFORM PRESENTATIONS
PLATFORM PRESENTATIONS SCHEDULE

8:40 – Robert Sinyard
Inter-Surgeon Variability for Outpatient ACL Repair: Implications for Cost and Operational Efficiency
Mentor: Chad Mather, MD
Dual Degree – MBA Study Program, Chad Mather, MD, Director

8:50 – Megan Para
Tissue Clearing to Examine Gut-Brain Connectivity
Mentors: Diego Bohorquez, PhD; Rodger Liddle, MD
Molecular Medicine – Nutritional and Metabolic Study Program, David Hsu, MD, Director

9:00 – Hussain Lalani
Evaluation of Intensive Care Unit Outcomes and Mortality at Moi Teaching and Referral Hospital in Kenya
Mentor: Peter Kussin, MD
Global Health Study Program, Dennis Clements, MD, Director

9:10 – Zachary Holcomb
Identification of Host-Derived Biomarker Signatures in Cryptococcal Infection
Mentor: Micah McClain, MD, PhD
Microbiology, Infectious Diseases and Immunology Study Program, Andrew Alspaugh, MD, Director

9:20 – Marguerite Cullen
ROPtool Analysis of Pictor Images in the Assessment of Plus and Pre-Plus Disease
Mentor: Catherine Bowes Rickman, PhD
Ophthalmology and Visual Science Study Program, Catherine Bowes Rickman, PhD, Director

9:30 – Jacqueline Henson
Equivalent Outcomes After Primary Liver Transplantation and Retransplantation for Disease Recurrence in Patients with Primary Sclerosing Cholangitis
Mentor: Andrew Muir, MD
Clinical Research Study Program, Vivian Chu, MD, MHS, Director

9:40 – Erwin Kong
Benefits of Training on a Novel Cognitive-Physical Video Game
Mentors: Joaquin Anguera, PhD and Adam Gazzaley, MD, PhD
Neuroscience Study Program, Christopher Lascola, MD, PhD, Director

9:50 – Monte Simms
The Dependency of Beta Cell Regeneration on Hyperglycemia: Are High Blood Glucose Levels Required to Generate New Beta Cells In Vivo?
Mentor: Larry Moss, MD
Microbiology, Infectious Diseases and Immunology Study Program, Andrew Alspaugh, MD, Director
10:00 – Emily Ngan
A Case-Control Study to Evaluate the Effectiveness of Maternal Tdap Receipt during Pregnancy in Preventing Infant Pertussis
Mentor: Geeta Swamy, MD
Microbiology, Infectious Diseases and Immunology Study Program, Andrew Alspaugh, MD, Director

10:10 – Ronnie Shammas
Human Adipose-Derived Stem Cells Labeled with Plasmonic Gold Nanostars for Cellular Tracking and Photothermal Cancer Cell Ablation
Mentors: Scott Hollenbeck, MD, and Gayathri Devi, PhD
Biomedical Engineering and Surgery Study Program, Bruce Klitzman, PhD, Director

10:20 – Kathleen Campbell
Quality Improvement of Screening for Autism in Primary Care
Mentor: Geraldine Dawson, PhD
Dual Degree – (CRTP, MPP, JD, MBA) Study Program, David Edelman, MD

10:30 – Sam Birer
Short and Long-Term Radiation Induced Damage to the Oral Mucosa is Prevented by a Mn Porphyrin SOD Mimic
Mentor: Mark Dewhirst, PhD
Molecular Medicine – Oncological Sciences Study Program, David Hsu, MD, Director
Inter-Surgeon Variability for Outpatient ACL Repair: Implications for Cost and Operational Efficiency
Robert D. Sinyard, Stephen R. Barchick, Richard C. Mather, MD, MBA

Background: Healthcare provider organizations have increasingly begun to interrogate their electronic medical record (EMR) systems to uncover opportunities for financial and operational efficiency in the setting of healthcare payment reform. Specifically in the realm of orthopedics, newly piloted bundled payments necessitate a clear understanding of bundled provider costs. The purpose of this study was to assess patient flow variability across several orthopedic surgeons performing anterior cruciate ligament (ACL) repair at an ambulatory surgery center and the impact of that variability on surgical personnel costs using a time-driven activity-based cost (TDABC) accounting methodology. Additionally, this study aimed to compare these costs to those of a prominent international hospital.

Methods: Process maps were developed for the entire ACL care cycle (preoperative, intraoperative, postoperative) by the involved staff. A representative sample of procedural time stamps from the electronic medical record was validated using direct observation. Analysis of variance (ANOVA) was used to compare EMR-generated timing data across 5 surgeons performing ACL repair for 577 patients. Furthermore, an analysis of case complexity was performed using the proxy of number of current procedural terminology (CPT) codes billed per case. Costs were determined by multiplying the cost capacity rate of each employee by the time involved in care delivery.

Results: Across the cohort of surgeons there was a significant difference in total cycle time (p < .0001). Such variability was driven primarily by variability in intraoperative time (p < .0001), operating room clean up time (p < .0001), and post-operative recovery time (p < .0001). There were no significant differences in check-in (p = .5863), pre-operative preparation (p = .2257), or operating room preparation time (p = .4485). For the 9 attending anesthesiologists involved, there was a significant difference in intra-operative time (p = .0336), but no significant difference in total care cycle time (p = .1229). Variability of case complexity by surgeon was significantly different (p < .0001), but increasing complexity scores were not directly aligned with increased intra-operative time. TDABC estimates of variability demonstrated that an increase of 10 minutes in the operating room led to an increase in personnel cost of $200. Total personnel cost were similar in magnitude to that of an internationally renowned hospital with a similar cost system performing the same procedure.

Conclusions: Analyzing variability in repetitive processes and removing “waste” is one step to improving operational efficiency and controlling costs. This study revealed substantial variability across five surgical colleagues at a large academic medical center with extensive experience and operative volume. Further, this study characterized the cost of that variability and indicated that such costs may be similar to those experienced by providers outside of the US. Pairing this type of process and true cost data with patient outcome data should guide care redesign efforts to maximize the value delivered per healthcare dollar spent.
Tissue clearing to examine gut-brain connectivity
Megan Para

Background: Sensory epithelial cells have long been recognized in multiple organs, from Merkel cells in the skin to hair cells in the inner ear. These specialized cell groups exist across the body with a common purpose: transduction of information about a sensory stimulus to the nervous system for processing. In the gastrointestinal tract, sensory epithelial cells called enteroendocrine cells share the same purpose. In contrast to the historical belief that enteroendocrine cells act only through production of hormones, our lab reported that these cells also synapse onto nerves; this finding correlates with the direct neural interaction displayed by sensory epithelial cells in other organs. The distribution and circuitry of these cells have not been mapped, particularly in the gastrointestinal epithelium.

Methods: To take advantage of modern optical sectioning for the gastrointestinal tract, we adapted a tissue-clearing protocol for removal of light-scattering lipid and pigment. This protocol was optimized to retain epithelial architecture, endogenous fluorescence, and antibody staining in the intact small intestine and colon. The clarified samples were then imaged with confocal microscopy and reconstructed in three dimensions using Imaris software. The protocol was also applied to neural tracing as a means to visualize fluorescent tracer in whole organs, particularly the colon and cervical nodose ganglion.

Results: Our optimized protocol allowed for a 3D, anatomically correct map of enteroendocrine cells throughout regions of the gastrointestinal tract. Applying our tissue clearing protocol in a tracing experiment, we visually mapped neuronal communication from colon to brain via the nodose ganglion of the vagus nerve.

Conclusions: By pairing modern optical techniques with an optimized tissue clearing protocol, we are able to examine gut sensory epithelial cells and their locations in three dimensions. Moving forward, such techniques for visualization will provide a platform to further characterize sensory epithelial cells, including the circuitry between these cells in the gastrointestinal tract and the central nervous system.
Evaluation of Intensive Care Unit Outcomes and Mortality at Moi Teaching and Referral Hospital in Kenya

Hussain S. Lalani,1,5 Wangari Waweru-Siika,2,3 Thomas Mwogi,2,3 Protus Kituyi,3,4 Peter S. Kussin1,2

1Department of Medicine, Duke University Medical Center; 2Academic Model Providing Access to Healthcare (AMPATH), Eldoret, Kenya; 3Department of Anesthesia, Moi Teaching and Referral Hospital and 4Moi University School of Medicine, Eldoret, Kenya; 5Doris Duke International Clinical Research Fellow

Background: The burden of disease in critical care is greatest in resource-limited countries (RLCs), and the adjusted risk of in-hospital death increases as the gross national income decreases. Intensive care unit (ICU) mortality rates vary from 9.3% in North America to 15.5% in Western Europe and are as high as 50.4% in East Africa. Access to critical care in sub-Saharan Africa (SSA) is limited due to numerous factors, including the high cost of care, lack of available technology, and limited ICU bed capacity. Mortality prediction tools have not been validated in the majority of RLCs. To date, ICU outcomes have not been described in Kenya, and given the recent initiative by the Kenyan Ministry of Health to expand ICU care across the country, such an analysis is timely. We examined ICU outcomes and mortality at Moi Teaching and Referral Hospital (MTRH), an 838-bed tertiary public hospital in Eldoret, Kenya, with a 6-bed mixed general ICU serving a catchment population of 15 million in western Kenya. We identified risk factors associated with higher and lower mortality, and validated the use of the Mortality-Prediction Model-II (MPM-II).

Methods: A retrospective observational cohort study of 450 patients admitted to the ICU at MTRH from January 1, 2013 to April 5, 2015 was performed. The primary outcome measure was ICU mortality, assessed at discharge from the ICU. Odds Ratio (OR) and two-sided Fisher’s exact test were performed to evaluate risk factors. Receiver Operating Characteristic (ROC) curve was used for discrimination of MPM-II while Hosmer-Lemeshow (HL) Goodness-of-Fit test was used to assess calibration of the model.

Results: 671 patients were admitted during the study period and 450 charts were analyzed. Median age was 29 years with a male to female ratio of 1.57:1, and 70.4% of patients were >=18 years. Median length of ICU stay was 4 days and the median cost of care per hospital admission was $1146. Admission diagnoses and interventions associated with the highest odds of mortality were Burns with > 10% body-surface-area (OR 9.95, p-value 0.0071), Acute Stroke (6.90, 0.0003), Sepsis (4.03, 0.0001), Intracranial Hemorrhage (3.06, 0.0149), Acute Renal Failure (2.41, 0.0229), Vasopressor use (8.76, <0.0001), and Mechanical Ventilation (4.80, <0.0001). Drug/alcohol intoxication (0.30, 0.0003) and Acute Guillain-Barre Syndrome (0.25, 0.0442) were associated with the lowest odds of mortality. Overall ICU mortality was 53.6%. Area under ROC curve for MPM-II discrimination was 0.78 (95% CI, 0.72 – 0.82) and HL chi-square statistic was 151.15 with p-value < 0.001 for calibration.

Conclusions: This is the first study to describe ICU outcomes in Kenya. The mortality rate of 53.6% is the highest reported in SSA. This suggests the need for targeted interventions to manage high-risk diagnoses and triage protocols to improve critical care outcomes. The MPM-II has acceptable discrimination with poor calibration, and is not valid at the study hospital. A site-specific model has the potential to assist with clinical decision-making.
Identification of Host-Derived Biomarker Signatures in Cryptococcal Infection

Zachary E Holcomb\textsuperscript{1,2}, Aimee K Zaas\textsuperscript{3,4}, Marisol Betancourt-Quiroz\textsuperscript{3}, John R Perfect\textsuperscript{3}, Micah T McClain\textsuperscript{3,4}

\textsuperscript{1}Duke University School of Medicine, Durham, NC
\textsuperscript{2}Eugene A. Stead Student Research Scholar, Durham, NC
\textsuperscript{3}Internal Medicine/Division of Infectious Diseases, Duke University Medical Center, Durham, NC
\textsuperscript{4}Center for Applied Genomics and Precision Medicine, Duke University

**Background:** Cryptococcal species cause invasive fungal infections capable of producing life-threatening complications, including pulmonary disease and meningoencephalitis. Understanding of the pathogenesis of disease and the host response to this fungal infection is still limited. We report the first peripheral blood gene expression analysis of the host response to infection with *Cryptococcus neoformans* (C. neoformans) and *Cryptococcus gattii* (C. gattii).

**Methods:** Forty-five BALB/cJ mice were challenged intranasally with *C. neoformans*, *C. gattii*, or sham control. The mice were followed serially and sacrificed 14 days post-infection. Whole blood was collected for transcriptomic analysis, along with various tissues to examine fungal burden. Differential gene expression was analyzed using Affymetrix microarrays. Functional gene expression pathway analysis was examined using Ingenuity Pathway Analysis (IPA) as well as the Database for Annotation, Visualization, and Integrated Discovery (DAVID). A disease classifier was developed using a Lasso multinomial regression model.

**Results:** The host peripheral blood transcriptomic response to *C. neoformans* was more robust than the response to *C. gattii* on the transcriptomic level, and mice infected with *C. neoformans* exhibited significantly higher organism burden in brain, lung, and splenic tissues. Significantly up-regulated genes in the infected mice clustered primarily into immune function pathways, including up-regulation of complement activity, skewing toward Th2-mediated immunity, and alternative activation of macrophages. A disease classifier composed of 27 unique genes accurately distinguished between infected and healthy control mice with a sensitivity and specificity of 100%.

**Conclusions:** Transcriptomic analysis demonstrates differences in both the character and magnitude of the host response to *C. neoformans* and *C. gattii* and provides insight into the mechanistic nature of these different host responses. The unique host response to Cryptococcal infection allows for development of a gene expression-based disease classifier that can successfully distinguish between infected and healthy mice. The host response to these organisms, as measured by gene expression in circulating white blood cells, proves useful both for improving our understanding of the unique pathophysiology of these infections, as well as potentially contributing to the development of future diagnostic assays based on gene expression-based biomarkers.
ROPtool analysis of Pictor images in the assessment of plus and pre-plus disease
Marguerite M. Cullen, BA, David K. Wallace, MD, MPH, Sharon F. Freedman, MD, S. Grace Prakalapakorn, MD, MPH

Background: Retinopathy of Prematurity (ROP) is a leading cause of preventable blindness in children. Plus disease is an essential component for determination of need for treatment, but diagnosis of plus disease is contested, even among ROP experts. ROPtool is a semi-automated computer program used to objectively measure retinal vascular characteristics in retinal images and has been validated to assess plus disease in RetCam and video indirect ophthalmoscopy images. Pictor is a hand-held, noncontact, narrow-field retinal camera. Our aim is to evaluate if ROPtool can accurately identify plus and pre-plus disease in a large set of Pictor images of varying qualities captured by non-physician health care workers (HCWs). While previous studies have used ROPtool to analyze single retinal images, we combined quadrant-level data from multiple Pictor images of a single retina to allow more quadrants to be analyzed.

Methods: As part of an ongoing prospective study, non-physician HCWs obtained Pictor retinal images of infants at risk for ROP during routine ROP rounds. Imagers selected 1-3 images per eye, aiming to show vessels in all 4 posterior pole quadrants. A non-physician HCW analyzed these images with ROPtool. Six measures reflecting vessel tortuosity and dilation were obtained per quadrant: tortuosity index (TI), maximum tortuosity (MT), dilation index (DI), maximum dilation (MD), sum of adjusted indices (SAI), and tortuosity-weighted plus (TWP). The reference standard was the diagnosis at the time of the clinical exam. Receiver operating characteristic (ROC) curves were generated for the identification of plus and pre-plus disease using the second-largest quadrant value of each measure, because plus disease requires that 2 quadrants have sufficient vascular abnormality. The area under the curve (AUC) was calculated for each measure for the identification of plus disease or the identification of plus or pre-plus disease.

Results: Of the 124 eyes imaged, 484 (98%) of 496 quadrants were analyzable by ROPtool, meaning they had at least one vessel traceable for at least one optic disc diameter in length. Overall, 92% of eyes had 4 analyzable quadrants, 6.5% had 3, and 1.6% had 2. For plus disease, AUCs were: TWP 0.97 > TI 0.97 > MT 0.96 > SAI 0.94 > DI 0.87 > MD 0.80. For pre-plus or plus disease, AUCs were: TWP 0.99 > MT 0.98 = TI 0.98 > SAI 0.945 > DI 0.86 > MD 0.80.

Conclusion: Pictor retinal images of varying qualities of infants at risk for ROP can be analyzed with ROPtool with high accuracy for the identification of plus and pre-plus disease. It is feasible for non-ophthalmologist HCWs to capture retinal images and analyze them for the presence of plus disease, furthering the available workforce for ROP screening.
Equivalent Outcomes After Primary Liver Transplantation and Retransplantation for Disease Recurrence in Patients with Primary Sclerosing Cholangitis
Jacqueline B. Henson, Shein-Chung Chow, Jiayin Zheng, Andrew J. Muir

**Background:** Primary sclerosing cholangitis (PSC) is an autoimmune, cholestatic liver disease with no available treatment besides liver transplantation (LT). Unfortunately, PSC may recur in up to 20% of LT recipients at five years, and recurrence increases the risk of graft failure and mortality. If graft failure occurs, whether due to disease recurrence or another cause such as primary graft nonfunction, vascular thrombosis, biliary complications, or rejection, repeat liver transplantation (re-LT) may be performed. Re-LT has been a controversial practice, however, due to its well-established inferior survival and the scarcity of organs available for LT. Attempts have therefore been made to identify patient subgroups or risk factors associated with poor outcomes, but the outcomes of re-LT in patients with PSC, and re-LT for PSC recurrence in particular, have not been well characterized.

**Methods:** The United Network for Organ Sharing database was retrospectively reviewed to identify all primary LTs in adults with PSC and subsequent first re-LTs between 1987 and 2015. Comparisons of clinical characteristics were made using chi-square tests or Fisher exact tests for categorical variables and t-tests or Wilcoxon rank-sum tests for continuous variables. Graft survival curves were computed using Kaplan-Meier methods and compared using log-rank tests. Cox proportional hazards regression was performed to adjust for donor and recipient factors that may affect graft survival.

**Results:** A total of 5,080 adults underwent primary LT for PSC, and 636 of the 1,803 (35.3%) who experienced graft failure underwent re-LT. Disease recurrence was the second most common indication for re-LT (178/564 with a reported cause of graft failure) and occurred at a median of 2,519 days (IQR 1,523-3,513) after the initial LT. Baseline characteristics at the time of transplantation for primary LT, all re-LTs, and re-LT for PSC recurrence are shown in the table. Five-year graft survival after re-LT was overall inferior compared to primary LT (63.9% vs. 76.6%, p=0.001). However, five-year graft survival after re-LT for disease recurrence was equivalent to primary LT (73.6% vs. 76.6%, p=0.45) and superior to other indications for re-LT (73.6% vs. 59.1%, p=0.001). The risks of graft failure after adjustment for donor and recipient characteristics were: re-LT vs. primary LT, HR 1.47, 95% CI (1.25-1.72); re-LT for recurrence vs. primary re-LT, HR 1.05, 95% CI (0.76-1.45); re-LT for recurrence vs. other re-LT, HR 0.62, 95% CI (0.43-0.90).

**Conclusions:** Though survival after re-LT was overall inferior to primary LT in patients with PSC, outcomes after re-LT for PSC recurrence were equivalent to primary LT at five years. Re-LT should thus be pursued in these patients in the appropriate clinical circumstances.

<table>
<thead>
<tr>
<th></th>
<th>Primary LT</th>
<th>All Re-LT</th>
<th>p</th>
<th>Re-LT for Recurrence</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>48 (38-57)</td>
<td>46 (36-55)</td>
<td><strong>0.001</strong></td>
<td>47 (38-56)</td>
<td>0.44</td>
</tr>
<tr>
<td>Male sex</td>
<td>68.0 (3453)</td>
<td>72.8 (458)</td>
<td><strong>0.01</strong></td>
<td>75.3 (134)</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>In ICU</td>
<td>7.4 (377)</td>
<td>29.1 (183)</td>
<td><strong>0.001</strong></td>
<td>11.8 (21)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>2.0 (100)</td>
<td>16.2 (102)</td>
<td><strong>0.001</strong></td>
<td>5.6 (10)</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>6.4 (2.7-15.0)</td>
<td>10.8 (3.3-24.2)</td>
<td><strong>0.001</strong></td>
<td>13.3 (5.4-26.5)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.9 (0.7-1.2)</td>
<td>1.3 (0.9-2.2)</td>
<td><strong>0.001</strong></td>
<td>1.4 (0.9-2.5)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.0 (2.5-3.5)</td>
<td>2.8 (2.4-3.3)</td>
<td><strong>0.001</strong></td>
<td>2.8 (2.3-3.4)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Data are presented as median (IQR) or % (n). P-values for comparison to primary LT.
Benefits of training on a novel cognitive-physical video game
Erwin L. Kong, Caleb A. Khan, Joshua J. Volponi, Juliana Souza, Roger Anguera, Christian J. Thompson, Joaquin A. Anguera, Adam Gazzaley

Background: Cognitive training interventions and physical exercise are two approaches that have been successfully used to enhance deficient cognitive control abilities across a variety of populations. Given that each approach has led to improvements in untrained cognitive abilities, the possibility exists that a synergistic effect on these abilities may be attainable through the combination of each training approach. The purpose of this study was to assess both physiological and cognitive adaptations associated with 8 weeks of training on a novel video game, “Body-Brain Trainer,” that combines both cognitive and physical training in a proportional fashion from an embodied cognition framework.

Methods: 38 young adults were randomized to either the training group (BBT, n=18) or the Control group (n=20). BBT completed 8 weeks of training, 3 days per week (24 sessions total) on the Body-Brain Trainer video game, comprised of nine 4-minute game play sessions combining both cognitive and physical training. The Control group trained on unrelated tablet-based games, which also consisted of cognitive and physical training, but never combined. Physical task difficulty and cognitive task difficulty in BBT adapted to the participant’s performance using real-time heart rate measures and cognitive performance metrics, respectively. Cognitive assessments were performed both before and after the training period, including: behavioral and neural measures of working memory, sustained attention, and goal management. Physical assessments were also performed at both time points, including: BMI, resting blood pressure, body composition by skinfolds, vertical jump, Hexagon Agility Test, and VO2 max via a treadmill ramp protocol.

Results: Repeated measures ANOVA analyses showed that training resulted in a significant decrease in systolic blood pressure in BBT (pre-training=121.83±11.99 mmHg, post-training=112.94±9.70 mmHg, p<0.01) compared to Control (pre-training=114.42±6.76 mmHg, post-training=115.58 mmHg±7.97). Body fat significantly decreased in BBT (pre-training=23.25±7.89, post-training=22.46±7.79, p=0.02), compared to Control (pre-training=22.5±5.87, post-training=23.63±5.80). Vertical jump significantly improved in BBT (pre-training=15.53±3.23 inches, post-training=16.19±3.11 inches, p=0.03) compared to Control (pre-training=16.71±3.88 inches, post-training=16.74±3.81 inches). However, VO2 max did not change in either group. ANCOVA analyses showed significant effects of BBT training on various measures of attention using the Test of Variable Attention (TOVA). TOVA False Alarm Rate was significantly lower in BBT group compared to Control, F(2,27) = 11.57, p <0.01. D’ was significantly higher in BBT compared to Control, F(2,33) = 5.099. Lastly, BBT showed greater accuracy compared to Control F(2,26)=8.184, p<0.01.

Conclusion: This novel video game integrating both exercise and cognitive challenges revealed potential improvements in both cognitive and physiological outcome measures. Future endeavors include examination of neural measures associated with training, enrollment of mechanistic control groups to characterize the effects of physical and cognitive training alone, and testing the game as a potential intervention in older adults for age-related cognitive decline.
The Dependency of Beta Cell Regeneration on Hyperglycemia: Are High Blood Glucose Levels Required to Generate New Beta Cells In Vivo?
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Background: Diabetes is a disease characterized by hyperglycemia secondary to insulin insufficiency that results from pancreatic beta cell failure. In humans, there is no significant level of beta cell regeneration and therefore patients with diabetes require lifelong therapy. In zebrafish, however, damaged beta cells do regenerate. This remarkable capacity makes the zebrafish a superior model for studying the regulatory mechanisms of regeneration. Understanding these mechanisms can guide the development of treatments for patients with diabetes. The role of blood glucose in beta cell regeneration of the adult zebrafish is currently unknown. Our study aims to determine if hyperglycemia is necessary to generate new beta cells in vivo in the adult zebrafish.

Methods: We used a transgenic construct to fluorescently label and selectively ablate beta cells in adult zebrafish. The transparent casper zebrafish strain was used to visualize the destruction and regeneration of beta cells in living fish. To reduce blood glucose following ablation, we gave a three-day course of two glucose-lowering agents. The first drug tested was insulin glargine. In addition, to remove insulin action as a confounding variable we tested a second drug, canagliflozin, which has an insulin-independent mechanism. Canagliflozin inhibits the sodium-glucose co-transporter 2 in the kidney thereby preventing glucose reabsorption. To assess drug efficacy, blood glucose measurements were taken following administration. To determine the effect of reduced blood glucose on subsequent beta cell regeneration we performed live imaging of fluorescent beta cell mass, serial blood glucose measurements, and islet immunofluorescence at critical time points during regeneration.

Results: Treatment with either glargine or canagliflozin reduced blood glucose levels when compared to the control group. Canagliflozin, however, also caused a transient rise in blood glucose immediately after administration. Fish that had received either glargine or canagliflozin to lower blood glucose initially remained hyperglycemic at later time points when the control group had returned to normal levels, indicating inhibition of full regeneration. Regeneration was more significantly inhibited in the glargine-treated fish than in canagliflozin-treated fish.

Conclusions: Lowering blood glucose with either glargine or canagliflozin during the three days following beta cell ablation blunts regeneration, and more dramatically so with glargine. This suggests that hyperglycemia during this period may be required for complete beta cell regeneration. Additionally, the acute hyperglycemia following canagliflozin treatment suggests possible glucagon-stimulated hepatic glucose production, which has also been observed in human patients receiving drugs of the same class. This transient increase in blood glucose could explain the less severe blunting seen with canagliflozin. Taken together, these results indicate hyperglycemia may be a critical driving factor in beta cell regeneration.
A Case-Control Study to Evaluate the Effectiveness of Maternal Tdap Receipt during Pregnancy in Preventing Infant Pertussis
Emily Ngan

Background: Whooping cough, a highly contagious respiratory disease caused by *Bordetella pertussis*, is characterized by prolonged cough, inspiratory whoop, paroxysmal cough, and posttussive emesis. Pertussis can be a severe and sometimes fatal disease in infants <1 year of age who are not fully protected by vaccination. One strategy to protect this vulnerable population is maternal Tdap vaccination during pregnancy. Maternal vaccination results in transplacentally transferred maternal antibodies that may protect infants against pertussis before DTaP-induced immunity is achieved. The CDC recommends Tdap vaccine be administered during the 27<sup>th</sup>-36<sup>th</sup> week of gestation of each pregnancy to maximize the transfer of vaccine-induced antibodies. Despite much research focused on evaluating maternal antibody transplacental transfer and vaccine safety in pregnancy, few studies have demonstrated the effectiveness of maternal vaccination in preventing infant pertussis.

Methods: A retrospective matched case-control study was conducted. Cases included all infant (<1 year) pertussis cases reported in North Carolina with onset dates between January 1, 2014 and December 31, 2015 (n=108; 2014 (84), 2015 (24)). Two controls per case were identified and matched according to month/year of birth and county of residence at the time of birth through birth records available from North Carolina Vital Records. Potential participants were sent a brief introductory letter and then contacted by the study team for telephone interview. Data included information on prenatal care, self-reported maternal Tdap vaccination, and sources of passive and active infant immunity, including DTaP administration, breastfeeding, daycare history, household contacts, and sick contacts (cases only). Official vaccination records were obtained from obstetric providers and pediatricians if records were not available through the North Carolina Immunization Registry.

Results: 33/108 cases and 23 matched controls were enrolled. There was a significant difference between type of prenatal care setting in cases and controls (p=0.0047), with cases more likely to have received care in a public clinic (any government-funded health institution) as compared to controls. There was no difference between self-reported receipt or declination of maternal Tdap vaccination (p=0.087 and p=0.209, respectively). Notably, the number of household occupants during the first year of life was significantly higher in case households as compared to control households (p=0.0006). The proportion of mothers who self-reported unknown Tdap vaccination during pregnancy, that their child had received at least one dose of the DTaP vaccine, breastfeeding during the first year of life, or placing their infant in daycare within the first year of life, did not differ between cases and controls.

Conclusions: Although there was no difference in self-reported maternal Tdap vaccination between cases and controls in this study, the significantly larger proportion of cases receiving care in public clinics and the greater number of household occupants in case versus control households points to an underlying difference between these two populations. Public clinic prenatal care is tightly associated with lower socioeconomic status, often leading to neonatal care in crowded households, which increases the risk of pertussis infection and spread. Maternal vaccination may protect these vulnerable infants in the presence of sick household contacts prior to adequate maturation of the neonatal immune system.
**Human Adipose-Derived Stem Cells Labeled with Plasmonic Gold Nanostars for Cellular Tracking and Photothermal Cancer Cell Ablation**


**Background:** Approximately 40,000 women in the U.S. die from breast cancer annually despite advances in chemotherapy, demonstrating the need for a novel class of therapeutic agents. Nanoparticles are one such agent with promising applications in cancer diagnostics and treatment. Gold nanostars (GNS) are unique nanoplatforms that transform light energy into heat to ablate cells and can be imaged in real time. The precision of nanoparticle delivery is greatly increased when a carrier that migrates specifically toward tumor niches delivers the GNS. In this study, we use the adipose-derived stem cell (ASC), which responds to chemokines secreted by tumors, as a vehicle for GNS delivery to breast cancer cells. Current obstacles to stem cell and nanoparticle therapies include inadequate intensity on imaging, rapid fluorescent signal decay, and uneven nanoparticle distribution throughout the tumor when administered systemically. The ability of ASCs to migrate towards and integrate into tumors makes them ideal vehicles for the targeted delivery of nanoparticles, establishing the foundation for GNS-labeled ASCs as a nanoparticle-based cancer therapeutic.

**Methods:** To test the labeling efficiency of GNS vs. Qtracker (the current gold standard), undifferentiated ASCs were incubated for 24 hours with GNS or Qtracker, fixed on day 1, 2, or 4, and imaged with multiphoton microscopy to monitor two-photon photoluminescence (TPL). The effects of GNS on cell phenotype, viability, and proliferation were assessed using flow cytometry, trypan blue, and MTT assays respectively. Next, GNS-ASCs were assessed for tri-lineage differentiation capacity and TPL throughout differentiation. For cellular ablation, photothermolysis was performed on ASCs alone to optimize the treatment power, then applied to GNS-ASC / SKBR3 cancer cell co-cultures using a laser power of 3.7 mW.

**Results:** Over 4 days of cellular proliferation, GNS exhibited stronger TPL than Qtracker. GNS did not affect cell phenotype, viability, proliferation, or tri-lineage differentiation. GNS exhibited stronger TPL than Qtracker throughout differentiation and could be seen after 21 days. Complete zones of ablation were observed following photothermolysis of GNS-ASCs, and the circumferential area of ablation increased with power and treatment time. At a power of 3.7 mW, photothermal activation of GNS-ASCs efficiently ablated co-cultured SKBR3 breast cancer cells.

**Conclusion:** These studies show that gold nanostars effectively label adipose-derived stem cells without altering their phenotype. Once labeled, laser photoactivation of GNS-ASCs ablates neighboring cancer cells, demonstrating the ability of ASCs to deliver site-specific cancer therapy. *In vivo* studies will use a mouse model of breast cancer to optimize tracking of GNS-ASCs following implantation and will further investigate the use of ASCs as a novel tumor-specific nanoparticle delivery mechanism for cancer therapy.
Quality Improvement of Screening for Autism in Primary Care
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Background: Early diagnosis and treatment for Autism Spectrum Disorder (ASD) improves clinical outcomes, yet it is challenging to identify children at risk for ASD by clinical judgement alone. Screening with the widely-accepted Modified Checklist for Autism in Toddlers – Revised with Follow up (M-CHAT-R/F) leads to early detection, but can be time-consuming and error-prone. Additionally, the low positive predictive value of screening tools has led to reluctance to refer children who screen positive for early diagnostic and intervention services. Therefore, there is a need for innovation in screening practices.

Methods: A multi-disciplinary team of clinic staff, autism researchers, and medical providers prospectively studied quality of screening for ASD in an academic primary care pediatrics clinic for 7 months prior to intervention. Quality metrics included accuracy of documentation of screening results and appropriate action for positive screens (secondary screening and referral). Researchers provided monthly feedback to the clinic on quality metrics and collected a survey on acceptability and perceived value of screening. The team then designed and implemented an intervention consisting of introduction of a tablet-based smart form version of the M-CHAT-R/F with automated scoring and risk assessment and continued feedback on quality metrics in the form of Plan-Do-Study-Act cycles for 7 months. Participating physicians were re-surveyed at the end of the study period to gauge acceptability of digital screening as well as changes in attitudes toward feasibility and value of screening for ASD. Evidence of change was evaluated with statistical process control charts and chi-squared tests.

Results: During the baseline period, quality metrics did not show significant change. Evidence of change reached statistical significance in the second and third month of intervention (2 of 3 subsequent points more than 2 standard deviations from the mean), and this change was sustained throughout the study period. In overall comparison of the baseline and intervention periods, accurate documentation increased from a mean of 54% to 92% (38% increase, 95% CI [14%,64%]) and appropriate action increased from a mean of 25% to 85% (60% increase, 95% CI [35%,85%]). On the physician survey, reported utilization of screening results for referral decision increased from 56% to 100%. 90% of participating physicians agreed that the transition to a digital screening form improved their clinical assessment of autism risk.

Conclusions: Implementation of a tablet-based smart form M-CHAT-R/F and feedback on progress led to improved feasibility and acceptability of screening for ASD. Quality metrics demonstrated significant change in physicians’ use of the screening instrument for risk assessment and referral decisions. As a result, the practice agreed to continue supporting this innovation and took steps to integrate these efforts with other forthcoming improvements in care delivery. These kinds of technologic innovations in routine care can provide efficient and reliable risk classification, and preserve physician time for direct patient care. Continued measurement of physician adherence to best practices and process improvement could aid in efforts to study the impact of early screening for ASD on child outcomes.
Short and Long-Term Radiation Induced Damage to the Oral Mucosa is Prevented by a Mn Porphyrin SOD Mimic

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Background: Head and neck squamous cell carcinomas (HNSCC) have an incidence of 62,000 new cases (3% of all cancers) diagnosed in the United States annually, and radiation therapy (RT) is an important treatment modality for these patients. Although RT is effective in many cases, >90% of patients develop side effects as a result of their treatment, including dermatitis, xerostomia (loss of saliva production) and oral mucositis (inflammation and ulceration of the oropharyngeal and/or esophageal mucosa), and in at least two-thirds of patients these effects are classified as “severe.” Mucositis and xerostomia tend to develop in a sequential fashion on the order of weeks to months following initiation of RT, and pose a particular risk because they can interfere with oral intake. There are no FDA approved therapies for the management of mucositis, and the only approved drug for treating xerostomia, amifostine, has its own poor side effects and provides incomplete protection.

Normal tissue damage following radiotherapy (RT) to the head and neck involves a continuum of pathologic events to the mucosa and salivary glands. We examined the potential radioprotective effects of MnBuOE, a manganese porphyrin oxidative stress modifier, at three stages of normal tissue damage: early (leukocyte endothelial cell interactions), intermediate (mucositis), and late (xerostomia) following RT. We also studied potential tumor-protecting effects of MnBuOE.

Methods:

Normal Tissue Protection: Mice received 0 or 9 Gy RT to the oral cavity and salivary glands ± MnBuOE. Changes in leukocyte-endothelial cell interactions and oxidative stress markers were measured 24 hours after RT. At 11 days post-RT, mucositis was assessed with a cathepsin-sensitive NIR optical probe. Finally, histological analyses were conducted to assess extent of long term post treatment effects in the salivary gland at 12 weeks after RT.

Tumor control: Mice were implanted with FaDu human squamous cell carcinoma tumors in the right flank. One week after implantation, each mouse was randomized to treatment with MnBuOE or saline, which was administered 3x/week until the tumor reached its endpoint. After tumors reached 200 mm³, mice received a single i.p. dose of cisplatin followed by three daily fractions of RT. Tumor growth was tracked daily and the mice were monitored for side effects. Mice were euthanized upon the tumor reaching 1500 mm³ or 90 days following RT.

Results: MnBuOE reduced leukocyte-endothelial cell interaction in radiation treated tongue tissue within 24 hours of RT. MnBuOE treatment was also found to reduce mucositis and lessen the extent of xerostomia after RT. There is no statistically significant change in the growth curves of a HNSCC pre-clinical model with long term MnBuOE administration. There is no statistically significant change in the growth curves of a HNSCC pre-clinical model with long term MnBuOE administration.

Conclusions: MnBuOE treatment reduces the severity of RT induced normal tissue damage across the continuum of the pathologic process, that starts with induction of inflammation and ends in significant long term tissue damage, as is illustrated by xerostomia. Additionally, the protective effects of MnBuOE appear to be limited to normal tissue, as it did not reduce the antitumor effect of RT + cisplatin on a squamous cell head and neck cancer model.
POSTER PRESENTATIONS

2. **Perez Agaba** – Risk factor for stiffness after total knee arthroplasty

3. **Maria Andrews** – If you build it, who will come? A retrospective analysis of attendance at Bull City Fit

4. **Betty Ashinne** – Assessing association of diabetic retinopathy and vitamin D serum levels in Asian Indians with type 2 diabetes

5. **Andrew Atia** - Postoperative tissue oxygenation in DIEP versus msTRAM flaps

6. **Adeola Awodele** - Myopia prevalence, incidence and progression in Singaporean adolescents

7. **Swar Bajpai** - Perioperative blood transfusions and complications in total elbow arthroplasty

8. **Taylor Broome** - Detection of tumor-associated antigen-specific T-cell responses in glioma patients

9. **Heather Burrell** - Tobacco use and psychosis risk in persons at clinical high risk

10. **Godefroy Chery** - Impact of human leukocyte antigen (HLA) mismatching on lung transplants outcomes

11. **Naomi Chou** - Multimodality word-finding distinctions in pediatric cortical stimulation mapping

12. **Daniel Cunningham** - Evidence to guide opioid prescriptions after hip arthroscopy

13. **A. Kyle Davidson** - The dual RhoGEF Kalirin's role in atherosclerosis through macrophage-specific mechanisms

14. **Isaiah Davies** - An upright eyedrop bottle: accuracy, usage of excess drops, and contamination compared to a conventional bottle
15. **Sophia Dunworth** - Effects of high-intensity interval training (HIT) in a hyperoxic-hyperbaric environment on exercise performance at altitude

16. **Hysem Eldik** - Real-time continuous monitoring of subcutaneous tissue oxygenation

17. **Harrison Farber** - Bone marrow entrapment as a novel form of T cell dysfunction in patients and mice with glioblastoma

18. **Zachary Finn** - The majority of patients seek medical care shortly prior to an out of hospital cardiac arrest

19. **Abigail Fulp** - Differential expression of T cell receptor CXCR3 in preterm birth placentas

20. **Javier Galan** - Comparing health outcomes and primary care physician utilization among low-income adults with type 2 diabetes and/or hypertension receiving either standard or intensive care management

21. **Feven Getaneh** - A virus, a window and a gut-brain neurocircuit: Novel protocols for in vivo calcium imaging of visceral sensation

22. **Adam Glener** - Interfrontal angle in the measurement of outcome and relapse in metopic craniosynostosis: Utility and limitations

23. **Ajay Gopalakrishna** - Lifestyle factors and health-related quality of life in bladder cancer survivors: A cross-sectional study


25. **Jing Han** - Cytokine receptor knockdown via CRISPR/Cas9 for treatment of disc herniation-associated pain

26. **Morgan Hardy** - Understanding the characteristics of primary care patients with frequent emergency department use

27. **Michael Harowicz** – Can BI-RADS features on mammography be used as a surrogate for expensive genomic testing in breast cancer patients?
28. **Jamie Holtz** - New prognostic grade group (PGG) prostate cancer grading system: Can multiparametric MRI (mpMRI) and TRUS-guided biopsy accurately separate patients with low, intermediate, and high-grade cancer?

29. **Benjamin Hoover** - Three-dimensional nanostructure of the tuft cell

30. **Alexandra Horne** - Things that make people happy: The role of sensory health, cognition, and neural factors in older adults' perceptions about subjective well-being


32. **Kathryn Hutchins** - An automated assessment of speech patterns in parents of preschoolers with autism spectrum disorders using the language environment analysis (LENA) system

33. **Samara Jinks** - Mechanisms for poor hypertension control among urban African Americans: Examining the effect of patient perceptions on blood pressure self-management

34. **Abigail Johnston** - Ankle-brachial index, symptom classification, and perceived quality of life in peripheral artery disease

35. **Phillip Kemp Bohan** - Early analysis of laparoscopic common bile duct exploration simulation

36. **Collin Kent** - Evaluating the impact of tumor mutational load on response to immune checkpoint inhibition and radiotherapy in primary mouse models of soft tissue sarcoma

37. **Mary Labowsky** - Clinical implications of negative direct immunofluorescence (DIF) results in mucous membrane pemphigoid (MMP) with ocular disease

38. **Peter Liu** - Searching for organization in atrial fibrillation: Recurrence quantification analysis of intracardiac electrogram morphology and cycle length in patients undergoing atrial fibrillation ablation with focal impulse and rotor modulation

39. **Daniel Loriaux** - A functional analysis of mixed lineage leukemia protein 2 (MLL2) in neurogenesis and the translational potential of histone deacetylase inhibition
40. **Daniel Loriaux** - The influence of the menstrual phases on polysomnography

41. **Andie MacDonald** - Postdepletion T cell reconstitution in mice with heterologous persistent and latent viral infections

42. **Michael Maranzano** - Assessing life's simple 7 in a southeastern US cohort: Dietary patterns and cardiovascular disease

43. **Melanie Masoud** - Decreased number of neuropeptide Y positive interneurons in CA1 of the hippocampus in mouse model of alternating hemiplegia of childhood

44. **Rajvi Mehta** - Wireless web-based interactive control of optical coherence tomography with mobile devices

45. **Yoon Mun** - Role of iNOS in lung injury development after chlorine and hydrochloric acid exposure

46. **Ben Murray** - Why risk death for a cure? A survey of HIV patients

47. **Charmaine Mutucumarana** - Immune correlates and peripartum mother-to-child transmission (MTCT) of HIV-1 in the setting of antiretrovirals (ARVs)

48. **Divya Natesan** - Primary vs preoperative radiation for locally advanced vulvar cancer: A national Cancer Database (NCDB) analysis

49. **Lowell Nicholson** - A novel monocyte vaccine as a simple and highly efficacious immunotherapeutic for glioblastoma

50. **Matthew O’Sullivan** - Retinal ganglion cells control spatial patterning of astrocytes to guide angiogenesis during development

51. **Chinmay Paranjape** - Cartilage strain increased with increasing speed and duration of exercise

52. **Jong Park** - Loss of MAFB function in humans and mice causes Duane syndrome, aberrant extraocular muscle innervation, and inner-ear defects

53. **Benjamin Parker** - Free mitochondria are taken up by antigen presenting cells and increase activation

54. **Ashwin Peres-da-Silva** - What factors drive inpatient satisfaction after knee arthroplasty?
55. Scott Perkins - Bland embolization vs radioembolization for the treatment of HCC in cirrhotic patients: Impact on hepatic function

56. Lauren Pontius - Lymphovascular invasion is associated with compromised survival for papillary thyroid cancer

57. Luke Poveromo - Modifying hernia mesh design to improve device mechanical performance and promote tension-free repair

58. Umar Qadri - Role of post-translational modifier Hipk2 in acute myeloid leukemia

59. Sunny Qiu - Novel mouse model of dystonia

60. Michael Quist - The effect of sponge versus no-sponge placement of mitomycin-C on the outcomes of trabeculectomy with Ex-PRESS glaucoma filtration device

61. Michael Quist - The effect of scheduled ripcord removal on the outcomes of Baerveldt 350 implants

62. Adrian Randall - Computational integration of clinical and geographic data in a diabetic population

63. Neil Ray - Lowering the barrier of surgical endoscopy with a novel articulating retractor

64. Jeffrey Sakamoto - Integrating heart rate variability, vital signs, ECG, and troponin to triage chest pain patients in the ED

65. Maya Schueller - Extracorporeal membrane oxygenation in premature infants

66. Kevin Schwartz - Adoption factors and usage patterns of vendor-supplied mobile applications for interaction with the electronic health record

67. Mya Sendak - An examination of participation in youth programs for adolescents with chronic illness

68. Kun Wei Song - Evidence implicating distinct FGF13 isoforms in a human epilepsy syndrome

70. **Alissa Stavig** - Should physicians take societal cost into consideration?

71. **Conrad Stern-Ascher** - Subfoveal choroidal thickness and associated changes in women with severe preeclampsia

72. **Christopher Sterwald** - Frosted intellectuals: How Leo Kanner constructed the autistic family

73. **Vinayak Venkataraman** - Characterizing pulse deficits in atrial fibrillation using simple ECG features

74. **Zachary Walker** – Determining the prognostic value of cardiac MRI for patients with elevated cardiac troponins and no significant coronary artery disease

75. **Jennifer Wang** - Using hyperpolarized $^{129}$Xe MRI to visualize and quantify gas transfer in idiopathic pulmonary fibrosis

76. **Laura Wang** - Long-term furosemide exposure does not increase risk of abnormal newborn hearing screen in premature infants

77. **Timothy Wang** - An internally randomized control trial of radiation exposure using ultra-low radiation imaging (ULRI) versus traditional C-arm fluoroscopy for patients undergoing single-level minimally invasive transforaminal lumbar interbody fusion (TLIF)

78. **Mimi Xu** - Longitudinal reproducibility of spectral domain optical coherence tomography in children with physiologic cupping and stable glaucoma

79. **Arthurine Zakama** - Management of infertility in women with PCOS

80. **Hanci Zhang** - Exercise induced cartilage strain at the shoulder: A study *in vivo*

81. **Xintong Zuo** - Creating a biomarker burden and strength index to link serum metabolites and inflammatory marker levels with functional status of older adults with varying health conditions

82. **Bora Chang** – Precision medicine in point-of-care management of surgical complications
Technological innovations for assessing attitudes and implicit bias toward mental illness in low-resource settings: adaptation and piloting of computer-based Implicit Association Tests in Nepal

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Background: Negative attitudes among health workers toward persons with mental illness are a barrier to the delivery of mental health services. To date, assessment of health worker attitudes in low-resource settings has been limited to self-report stigma measures, which inconsistently predict clinical care. In high resource settings, computer-based Implicit Association Tests (IAT) are being used to assess the unconscious biases that influence behavior. Use of IAT in low-resource settings presents challenges including computer literacy, cross-cultural adaptation of stimuli, and stimuli presentation in non-Romanized scripts.

Methods: We used PsychoPy to develop an IAT measuring the participant’s association of mental vs. physical illness with safety vs. dangerous attributes. Nepali stimuli were developed using a combination of structured elicitation tasks. The IAT and a measure of social distance were administered to Nepali health care providers (n=200) on day 1 of a mental health training program.

Results: There was a moderate association of implicit biases with self-reported stigma measures. The association was strengthened when controlling for differences in computer literacy among health workers. We adapted administration to increase practice, which strengthened associations.

Conclusions: The correlation of the IAT \( d \) score to self-reported measures of social distance suggests a relationship between the implicit bias of danger and the likelihood of mental health provider social distance. Further, the correlation is suggestive of the positive validity of a violence/safety IAT in the assessment of Nepali mental health provider implicit biases. Next steps will include the testing of predictive validity, measuring the association of implicit biases with behavioral measures of mental health care competency.
Risk Factor Combinations For Stiffness After Total Knee Arthroplasty  
Perez Agaba

**Background:** Stiffness after Total Knee Arthroplasty (TKA) is an uncommon complication that can be treated with manipulation under anesthesia (MUA) in the early postoperative period. The purpose of this study was to assess the impact of various individual and combined demographic factors and comorbidities on the frequency of MUA following TKA.

**Methods:** We identified 123,728 TKA patients using a Nationwide Private Insurance Healthcare Database containing medical records of 19.6 million patients between 2007 and 2015. Demographics (age, race, gender) and comorbidities (smoking, diabetes, BMI, narcotic use, preoperative stiffness, hypertension, osteoarthritis, depression, hypercholesterolemia, rheumatoid arthritis/SLE, osteonecrosis) were stratified and their impact on the rates of MUA investigated. Odds ratios and 95% confidence intervals were used to assess the effect of individual and combined factors on MUA rates using Stata.

**Results:** Of the 123,728 patients, 3145 (2.54%) patients had an MUA within 90 days of TKA. Individual factors that were significantly associated with higher MUA rates include; African American (AA) (OR 1.37, 95% CI 1.23-1.54), BMI< 30 (OR 1.15, 95% CI 1.04-1.26), Age<60 (OR 2.15, 95% CI 1.97-2.34), and preoperative stiffness (OR 1.81, 95%CI 1.58-2.08). The combined factors significantly associated with higher MUA rates are: AA +, BMI<30, Age<60, (OR 5.18, 95%CI 3.24, 8.27). The combined protective factors are: Caucasian, BMI>30, Age>60 (OR 0.75, 95%CI 0.68, 0.82).

**Conclusions:** Our results show that BMI<30, age<60, and African American race have an additive effect towards MUA rates. The largest individual risk factor was age<60. Patients with RA/SLE, HTN and depression were less likely to develop stiffness. Diabetes, smoking, hypercholesterolemia, secondary osteoarthritis, and opioid abuse don’t have a significant effect on MUA rates. Patients who have multiple risk factors may benefit from preoperative counseling and close post-operative follow up by their physician.
**If you build it, who will come? A retrospective analysis of attendance at Bull City Fit**

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**Background:** Childhood obesity’s multifactorial nature makes treatment difficult. Duke Children’s Healthy Lifestyles pediatric weight management clinic (HL) has partnered with Durham Parks & Recreation to develop a wellness program called Bull City Fit (BCF), where HL patients can participate in fitness classes and wellness education. We sought to describe the general population of patients who opted to attend BCF between 2013-2015, and hypothesized that higher attendance would be seen in patients with shorter distances to travel, less impoverished neighborhoods (i.e. higher SES), and fewer comorbidities at baseline.

**Methods:** We conducted a retrospective chart review to identify patients aged 2-17 who enrolled in HL between June 1, 2013, and June 1, 2015, and attended BCF within 6 months. We analyzed their BCF attendance and compared demographic and clinical data across two cohorts: (1) high-attenders of BCF (>25 hours over 6 months) and (2) low-attenders (≤25 hours/6mo). Secondarily, BMI z-score and blood pressure were collected at baseline, 3 months, and 6 months and compared between high- and low-attenders. A descriptive analysis of baseline demographics, comorbidity types and prevalence, health habits, and participation rates was performed. Kruskal-Wallis statistical analysis was used to identify predictive factors of BCF attendance across a continuum of hours of participation.

**Results:** BCF served 171 children who met criteria for inclusion. A comparison of health outcomes and baseline characteristics showed that the mean age was 10 years (range 4-16); 55% were female; 46% were of Hispanic ethnicity, with 31% black, 12% white, and 57% mixed or other race. At baseline, 31.3% of subjects had a diagnosis of asthma and median HbA1C was 5.5%. Mean BMI z-score at start was 2.2 (range 0.9-4.5). For those with follow-up clinic data (n=76), mean 6-month z-score change was -0.05 (range -0.6-0.7). Subjects on average made 3.87 visits to the Healthy Lifestyles clinic in their first 6 months of enrollment, and an average of 12.95 check-ins at Bull City Fit over those same 6 months (<0.5 check-ins per week). Of the measures obtained, only lower parental weight, Spanish-as-a-preferred-language, low HL attendance, and baseline developmental disabilities were statistically significant indicators of higher attendance.

**Conclusions:** BCF is a feasible program to engage low income, racially diverse and non-native populations in child obesity treatment. Low attenders of BCF (≤25 hours/6 months) were more likely to have parents with higher BMI, have developmental disabilities at baseline, and attend fewer HL clinic visits than high attenders (>25 hours/6 months or ~1 hour/week). No significant differences in secondary outcomes (BMIz and SBP) were noted between low and high attenders, indicating that attendance is not necessarily a meaningful proxy for health outcomes. A prospective, randomized clinical trial is needed to assess the effectiveness of BCF in the integrated treatment of childhood obesity, and is in progress.
Assessing association of diabetic retinopathy and vitamin D serum levels in Asian Indians with type 2 diabetes
Betty Ashinne

**Background:** Diabetic retinopathy (DR) is the third main cause of vision loss in the United States and fifth leading cause both globally and in South Asian countries. Within the Asian Indian population with type 2 diabetes, more than half showed signs of DR within 10 to 12 years following their diagnosis. In the quest to understand risks and protective factors associated with various eye diseases, there has been interest in investigating serum 25-hydroxyvitamin D’s role in hindering pathologic vascularization. This has relevance for DR research since measures to minimize microvascular compromise could impact DR onset and progression. A study targeting Asian Indian adults is critical since India has the highest prevalence of diabetes globally and this prevalence is projected to rise to 87.0 million by 2030. Given this, our study aimed to evaluate the association of serum 25-hydroxyvitamin D levels with presence and severity of DR in the Asian Indian population with type 2 diabetes.

**Methods:** In this retrospective cohort study, we collected medical information on 3,054 patients with type 2 diabetes that received care at Dr. Mohan’s Diabetes Specialties Centre in Chennai, India. These study subjects were 18 to 89 years of age, had undergone retinal examinations with DR grading, had recorded measurements of serum 25-hydroxyvitamin D concentrations, and were not taking vitamin D supplements or multivitamins with over 1000 IU of vitamin D. Two sample T-test was used to compare serum 25-hydroxyvitamin D sample means of patients with versus without DR and one-way analysis of variance (ANOVA) was used to compare serum 25-hydroxyvitamin D sample means among patients with different DR grades. Analysis of quantitative study data was conducted in SAS, version 9.4 (SAS Institute, Cary, N.C).

**Results:** Among all study participants, mean serum 25-hydroxyvitamin D was 16.9±14.0 ng/ml. Mean value of serum 25-hydroxyvitamin D in patients without DR was higher than mean in patients with DR, 17.7±14.9 ng/ml vs 15.8±12.7 ng/ml, respectively (p = 0.0002). After stratifying patients based on their recorded DR grade, downward trend in mean values were noted: no DR (17.7±14.9 ng/ml), non-proliferative DR (16.4±13.0 ng/ml), and proliferative DR (12.9±10.3 ng/ml) (p <0.0001).

**Conclusion:** Our results suggest that, among Asian Indians with type 2 diabetes, an association exists between mean serum 25-hydroxyvitamin D and DR presence. Future studies are required to take into account the sample mean 25-hydroxyvitamin D (16.9±14.0 ng/ml) that lies in the range of vitamin d deficiency, i.e. values < 20.0 ng/ml.
Post-operative Tissue Oxygenation in DIEP versus msTRAM Flaps
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Background: A common etiology for free-flap failure is post-operative ischemia. As microvascular breast flap reconstruction continues to evolve, debate remains over tissue perfusion in deep inferior epigastric perforator (DIEP) vs. muscle sparing transverse rectus abdominus muscle (msTRAM) flaps. Recently, post-operative flap oxygenation measurement using percutaneous tissue monitoring has become available. We compared post-operative tissue oxygenation for DIEP versus msTRAM flaps. We hypothesized that msTRAM flaps would have higher oxygen saturation levels in the perioperative period.

Methods: A retrospective review was performed to identify all patients undergoing free-flap breast reconstruction for which tissue oxygenation was measured and recorded. Between November 2013 and January 2016, we identified 58 patients who underwent 96 abdominally based free-flap breast reconstructions for which tissue oxygenation was recorded on post-operative days (POD) 0-3 (Vioptic system). Mean oxygen saturation for each flap subtype was compared using a Student’s T-test.

Results: Of the 58 patients who were identified, 40 (69%) had bilateral flap reconstructions, while 18 (31%) had a unilateral flap reconstruction. Of the 96 free-flaps, 76 were DIEP flaps and 20 were msTRAM flaps. Of the 40 patients that underwent bilateral flap reconstructions, 9 cases were one-sided DIEP and one-sided msTRAM flaps. The mean number of perforators for DIEP and msTRAM flaps was 2.01 and 3.70, respectively (p=0.29). The mean starting oxygen saturation for DIEP and msTRAM flaps was 70.8% and 71.3%, respectively (p=0.79). PODs 0-3, the mean oxygen saturation did not significantly differ between DIEP and msTRAM flaps (70.74% versus 71.16%, p=0.57). The mean oxygen saturation of both flap types decreased slightly over time. Three flaps required unplanned post-operative exploration. None required excision due to flap failure.

Conclusions: In contrast to our hypothesis, we found no difference in early post-operative oxygen saturation between DIEP and msTRAM flaps. This suggests that the decision to perform DIEP versus msTRAM flaps leads to similarly perfused flaps based on available perforators. Additionally, there is minimal change in tissue oxygenation over the first three days for stable flaps.
Myopia Prevalence, Incidence and Progression in Singaporean Adolescents
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Duke-NUS Scholarship

Background
The Singapore Cohort Study of the Risk Factors for myopia (SCORM) is a longitudinal school-based study that recruited 1979 children, aged 7 to 9 years old between 1999 and 2001, who were re-examined as adolescents in 2006 and 2007. This current study is to determine the prevalence, incidence and progression of myopia among Singapore teenagers and describe any trend in the SCORM study.

Methods
At each visit, participants underwent comprehensive eye examinations that included cycloplegic autorefraction and ocular biometry measurements.

Results
The prevalence of myopia (SE<-0.5D) and high myopia (SE<-6.0D) among Singapore teenagers aged 11-18 years old was 69.1% [95% confidence interval (CI) 66.5-71.7] and 7.1% (95% CI 5.8-8.7), respectively, with the highest prevalence in people of Chinese ethnicity (p<0.001). The annual incidence was 13.7% (95% CI 9.8-17.6). Males had twice the incidence of females (p=0.043), and adolescents with longer axial lengths (p<0.001) and deeper vitreous chamber (p<0.001) had higher myopia incidence. Annual myopia progression was -0.32 Diopters (D) (SD=0.40), with no difference by age, race or gender. However, adolescents with higher myopia levels at 2006 had significantly faster myopia progression rates (p<0.001).

Conclusion
Myopia prevalence in Singapore teenagers, especially Singapore Chinese teenagers, is one of the highest in the world. In adolescents, there is still a high rate of new onset and rapid progression of myopia. These findings indicate that adolescence may still represent a viable period for intervention programs to mitigate myopia onset and progression.
Perioperative Blood Transfusions and Complications in Total Elbow Arthroplasty
Swara Bajpai

**Background:** Complication rates for total elbow arthroplasty (TEA) have not been well studied due to low utilization rates. The aim of this study was to analyze the rate of utilization of TEA and perioperative PRBC transfusion from 2005 to 2010, overall rates of surgical complications, and any association of perioperative PRBC transfusion with postoperative medical and surgical complications.

**Methods:** We queried a large, nationwide Medicare database from 2005 to 2012 utilizing PearlDiver Technologies (Warsaw, IN) to identify the index surgery, perioperative blood transfusions, and postoperative complications of interest. Incidence (IN), odds ratios (OR), 95% confidence intervals (CI), and p-values were calculated for 30-day, 90-day and 2-year complications.

**Results:** We identified a total of 7,125 TEA procedures with a minimum of 2-year follow-up. Utilization of TEA and blood transfusions remained stable over 5 years. Aside from DVT and PE’s, all medical complications including arrhythmia, anemia, acute renal failure, sepsis, heart and respiratory failure, etc. were significantly more common within 30 days post-op in patients receiving perioperative PRBC than not. For both 90 days and 2 years post-op, revision surgeries were significantly more common in patients who did not receive transfusions. In addition, infection-related complications were one of the most frequent complications overall with significantly higher rates occurring in transfused patients.

**Conclusions:** Surgeons should be aware that patients requiring transfusions after TEA may have higher rates of complications and should preemptively counsel patients during admission and at discharge. Further evidence is needed to determine whether post-operative transfusion is simply a marker of overall poor health or whether the transfusion also has an immuno-modulatory effect that increases the risk of medical and surgical complications.
Detection of tumor-associated antigen-specific T-cell responses in glioma patients

Taylor M. Broome

Background: Despite advances in cancer treatment, glioblastoma remains deadly with a median overall survival of 14.6 months. Immunotherapy has offered a promising alternative to standard of care treatment in glioblastoma, however, there have been significant challenges to measuring a robust immune response in glioblastoma patients. One such challenge is the inability to monitor low-level tumor responses by traditional immunomonitoring assays. A potential solution to this problem is to increase detection by clonally expanding tumor-specific T cell populations via cell culture.

Methods: Patient samples from two clinical trials, RESTART and CheckMate 143, were used for development of the methodology and evaluation of the method for immunomonitoring, respectively. The control was single-use aliquots of peripheral blood mononuclear cells (PBMCs) from normal CMV seropositive donors obtained from SeraCare Life Sciences. PBMCs were cultured with IL-2 and IL-15 for 10 days in the presence of peptide pools of tumor-associated antigens (TAAs). On day 10, cells were removed from culture and IFN-γ Enzyme-Linked ImmunoSpot (ELISpot), IFN-γ fluorospot, or dual IFN-γ/Granzyme B fluorospot assay was performed to quantify tumor-specific T cell responses. Data was analyzed using GraphPad Prism 5.0 and two-way ANOVA with Bonferroni post-test was used to compare groups.

Results: Of the cells cultured with peptide pools of TAAs, only SeraCare cells that were cultured and subsequently stimulated in IFN-γ ELISpot with HER2ECD (p < 0.001) and EGFR1 (p < 0.01) reached significance when compared to cells that were not cultured. RESTART patient 26 cells cultured with TAAs and submitted to the IFN-γ ELISpot and dual fluorospot did not reach significance, but were qualitatively increased compared to uncultured cells. Responses of RESTART patient 12 cells cultured with HER2ECD showed much greater responses when stimulated in IFN-γ ELISpot with HER2ECD (p < 0.05) compared to stimulation of cells alone with HER2ECD. Additionally, cells cultured with HER2ECD showed only low level responses when stimulated with EGFR1 during IFN-γ ELISpot, which is indicative of the specificity of the response to HER2ECD. When samples from patient 3 and 5 of CheckMate 143 were compared over time via IFN-γ and dual fluorospot, there were qualitative differences between the tumor responses over time. This has potential as a target for immune monitoring. Additionally, when tumor-infiltrating lymphocytes (TILs) and PBMCs from patient 3 were compared via IFN-γ ELISpot, responses to TAAs (p < 0.001) and CEF (p < 0.05) were significant between groups. This supports the monitoring of TAA-specific tumor responses, peptide pools of TAAs and PBMCs for immune monitoring.

Conclusion: Culturing patient PBMCs and TILs prior to ELISpot or fluorospot is an acceptable method for enhancing the detection of tumor-specific responses for immunomonitoring. Larger sample size will allow us to further solidify our conclusions.
**Tobacco Use and Psychosis Risk in Persons at Clinical High Risk**

**Background**: One of the most consistent observations in persons with schizophrenia and other psychotic disorders is a high rate of tobacco use, estimated at 3- to 6-fold that of the general population. Initiation of smoking occurs before psychosis symptoms emerge for about 75% of persons with schizophrenia, and prospective population-based cohort studies find that risk of schizophrenia is about doubled for tobacco smokers. Based on the observed temporal precedence and that higher levels of tobacco use are associated with higher risk of subsequent schizophrenia, several researchers propose that there is a causal relationship between smoking tobacco and the development of a psychotic disorder. These same investigators acknowledge, however, the many challenges to establishing causality in observational studies, especially that of confounding. Factors associated with increased risk of smoking initiation and dependence in the general population, if also associated with psychosis-risk, could confound associations of smoking and schizophrenia. General population factors associated with smoking include depression, anxiety, low self-esteem, impulsivity, trauma, stress, alcohol use, poor academic performance, and low socioeconomic status. The purpose of this study was to evaluate the role of tobacco use in the development of psychosis in individuals at clinical high risk.

**Method**: The North American Prodrome Longitudinal Study is a 2-year multi-site prospective case control study of persons at clinical high risk that aims to better understand predictors and mechanisms for the development of psychosis. The cohort consisted of 764 clinical high risk and 279 healthy comparison subjects. Clinical assessments included use of tobacco and other substances and several risk factors associated with smoking in general population studies.

**Results**: Clinical high risk subjects were more likely to smoke cigarettes than unaffected subjects (Light Smoking OR=3.0, 95%CI=1.9-5; Heavy Smoking OR=4.8, 95%CI=1.7-13.7). In both groups smoking was associated with substance use, stressful life events, and perceived discrimination and in clinical high risk subjects with childhood emotional neglect and adaptation to school. Clinical high risk subjects reported higher rates of several factors known to be associated with smoking, including substance use, anxiety, trauma, and perceived discrimination. The relationship between clinical high risk state and smoking became non-significant after controlling for these potential confounders (Light Smoking OR=1.9, 95%CI=0.7-5.2; Heavy Smoking OR=0.9, 95%CI=0.1-7.2). Moreover, smoking status at baseline (HR=1.16, 95%CI=0.82-1.65) and categorization as ever-smoked (HR=1.3, 95%CI=0.8-2.1) did not predict time to conversion.

**Conclusions**: Our study did not support a causal relationship between smoking and psychosis. Rather, increased proportions of smokers in persons at clinical high risk appears to be related to elevations of factors associated with tobacco use generally.
Impact of Human Leukocyte Antigen (HLA) Mismatching On Lung Transplants Outcomes.

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Background: The significance of the human leukocyte antigen (HLA) donor-recipient mismatching on survival and development of chronic lung allograft dysfunction (CLAD) after lung transplantation remains unclear, as previous studies have reported inconsistent findings, possibly due to small datasets and limited outcome data. We sought to assess the impact of total HLA donor-recipient mismatch and specific locus (A, B, DR) mismatch on survival and development of chronic lung allograft dysfunction (CLAD) in a well-defined cohort.

Methods: All lung transplant recipient and donor HLA information was analyzed for total and individual locus (A, B, DR) donor-recipient mismatch (dichotomized as ≤ 4 vs 5-6 and as 2 vs. 0–1, respectively). Cox proportional hazard regression models were used to assess the impact of HLA mismatch on survival and time to CLAD onset.

Results: There were 1,379 first lung recipients eligible for the survival analysis. In our multivariate analyses, total HLA mismatch was associated with worse survival (HR=1.16; 95% CI 1.00 to 1.34; p=0.037). HLA mismatch at the HLA-DR locus was also associated with worse survival. Specifically, compared to subjects with 0-1 mismatch, subjects with 2 mismatches at the HLA-DR locus had worse survival (HR=1.23; 95% CI 1.07 to 1.42; p=0.004). Furthermore, individual HLA mismatch at loci A, and B were not significantly associated with worse survival (HLA-A locus HR=1.04; 95% CI 0.90 to 1.20; p=0.58. HLA-B locus HR=1.27; 95% CI 0.97 to 1.31; p=0.127). Of the 998 recipients eligible for CLAD analysis, total HLA mismatch was not significantly associated with the development of CLAD (HR=1.15; 95% CI 0.98 to 1.45; p=0.06) or mismatch at the HLA-A locus (HR=1.24, 95% CI 0.93 to 1.35; p=0.22), HLA-B locus (HR= 1.04, 95% CI 0.85 to 1.26, p=0.69), or HLA-DR locus (HR= 1.09, 95% CI 0.90 to 1.32, p=0.34).

Conclusion: In this well-defined cohort with extended follow-up, total HLA mismatch and mismatch at the DR-locus had a statistically significant association with worse survival. However, individual mismatch at the A, B loci were not associated with worse survival. In addition, total HLA mismatch and individual mismatch at the A, B and DR loci were not associated with the development of CLAD.
Multimodality word-finding distinctions in pediatric cortical stimulation mapping
Chou, Naomi; Serafini, Sandra; Clyde, Merlise; Grant, Gerald; Komisarow, Jordan; Muh, Carrie

**Background:** Recently, auditory naming has been added to cortical stimulation mapping (CSM) to provide a comprehensive language map prior to resection in epilepsy patients. Modality-specific language sites have been found using CSM in adult epilepsy patients, but research in the pediatric population is limited. Here we demonstrate distinctions between visual and auditory modalities and identify where errors are most likely to occur in pediatric patients.

**Methods:** A series of twenty-one pediatric epilepsy patients (15 female; M age 12.4±3.1 years, 6.6-17.4 years) underwent CSM using visual (n=21) and auditory (n=13) naming paradigms. Mixed effects logistic regression was used with the response being the indicator of an error on an individual trial. We adjusted for patient-specific effects using random effects, and included fixed effects for Region, Modality, interactions between Modality and Region, and Age <13 years.

**Results:** No evidence was found to support differences in errors due to age. Statistically significant differences were found by Modality, with auditory naming having a 1.43 higher odds of identifying errors (95% CI 1.10, 1.87, \( p = 0.0085 \)) compared to visual naming. Probabilities of visual and/or auditory naming errors varied significantly among regions (\( p = 0.00199 \)). Figure 1 shows a heat map of error probabilities within each subregion for visual and auditory naming. The highest probability of detecting an error was in the PolMTG under visual naming modality and in MPrG under auditory naming modality (0.90 and 0.80 respectively).

**Conclusions:** The auditory naming modality is more sensitive in detecting errors than visual naming in pediatric epilepsy patients. The PolMTG region shows the most naming errors in visual naming and the MPrG region shows the most naming errors in auditory naming regardless of age, suggesting that CSM mapping with both modalities across the temporal lobe and posterior frontal lobe is necessary to obtain a comprehensive language map prior to resection.

Figure 1. Heat map of error probabilities within each subregion for visual and auditory naming.
Evidence to Guide Opioid Prescriptions after Hip Arthroscopy
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**Background:** In response to the prescription opioid abuse epidemic, the American Academy of Orthopaedic Surgeons’ Information Statement on Opioid Use, Misuse, and Abuse advocates for evidence-based, standardized opioid prescription protocols. Additionally, the statement supports using predictive metrics to identify patients at risk for opioid use and abuse. Although the number of hip arthroscopies performed each year increased 18-fold between 1999 and 2009, there are currently no evidence-based guidelines for opioid prescription patterns after hip arthroscopy for symptomatic femoroacetabular impingement (FAI). To address this, we evaluated factors that affected opioid usage after hip arthroscopy.

**Methods:** Patients 18 years of age or older scheduled to undergo hip arthroscopy for symptomatic FAI with either of 2 hip preservation surgeons at Duke University Medical Center were approached to consider participating in this IRB-approved study. Consented subjects answered questions regarding pre-operative pain, function, and psychological status including opioid and anti-inflammatory medication usage, gender, the International Hip Outcome Tool (iHOT-12), visual analog scale (VAS) pain, Pain Catastrophizing Scale (PCS), and abbreviated Patient Health Questionnaire (PHQ-8). After surgery, patients recorded daily opioid usage up to the first post-operative visit in a study-provided diary. At the 2-week and 6-week post-operative visits, pain medication usage was measured through pill counting. Univariate tests of significance were carried out between the pre-operative covariates and the outcomes of 2-week opioid usage, 6-week opioid usage, and the time to the patient’s first day off of opioids. Those pre-operative covariates with p-value less than 0.15 were incorporated into multivariable models of the outcomes. Predictors in multivariable models with p-value less than 0.05 are reported as significant below.

**Results:** In a complete case analysis of 40 diaries, 39 completed 2-week pill-counts, and 26 completed 6-week pill-counts, the median patient used 10 (3,31) [median (Q1,Q3)] opioid pills over the first two weeks and 10 (2,30) opioid pills over the first 6 weeks. Pre-operative opioid usage significantly correlated with all 3 outcomes: 2-week total opioid usage (p=0.0027), 6-week total opioid usage (0.0006), and delay to first day using no opioids (p=0.0002). Patients with pre-operative opioid usage took 54 (43,59) pills by 2 weeks and 80 (70, 91) pills by 6 weeks, while patients without pre-operative opioid usage took 7 (1,18) pills by 2 weeks and 6 (1,21) pills by 6 weeks. 83% of patients with pre-operative opioid usage failed to achieve a single day without opioid usage between surgery and their first post-operative visit compared to only 9% of patients without pre-operative opioid usage. None of the other covariates significantly impacted the multivariable models.

**Conclusion:** Establishing evidence-based opioid prescription guidelines is critical. This is the first study in FAI treatment to correlate pre-operative predictive factors to post-operative pain medication usage. Patients not taking opioids pre-operatively used only 6 pills by 6 weeks compared to 80 pills for patients with pre-operative usage. Measurement of this binary risk factor can likely be implemented without substantial increased clinical time and could prompt the clinician to prescribe far less opioids for patients without pre-operative usage.
The dual RhoGEF Kalirin’s role in atherosclerosis through macrophage-specific mechanisms
A. Kyle Davidson, Eugene A. Stead Scholarship Recipient

Background: Atherosclerosis is the principal cause of myocardial infarction and stroke, which together cause more deaths in industrialized countries than any other diseases. There are many genes suspected to play a role in disease progression, but many remain incompletely understood. One such gene known to associate with human atherosclerosis (athero) is KALRN, which encodes the ~270 kDa protein Kalirin comprising two GTP exchange factor (GEF) domains, Rac1 and RhoA. KALRN is expressed in many tissues involved in atherosclerotic plaque development, including endothelial cells, smooth muscle cells, and macrophages (Mφ). Our lab has previously shown in Mφs that physiologic levels of Kalirin inhibit the pro-atherogenic activity of inducible nitric oxide synthase and promote the secretion of the anti-atherogenic cytokine interleukin 10 (IL-10). We hypothesized that Kalirin reduces athero by promoting IL-10 secretion in macrophages.

Methods: Mouse Mφs were harvested from bone marrow of Kalrn+/+ and Kalrn−/− mice. Bone marrow-derived macrophages (BMDM) were stimulated with LPS or MCP-1 in all in vitro experiments. Relative amounts of phospho- and total protein were assessed by immunoblotting followed by quantitation of protein band density (Image Lab). Rac1 G-LISA or RhoA G-LISA was performed on stimulated BMDMs and the amount of Rac-GTP or RhoA-GTP was assessed colorimetrically. IL-10 and IL-6 secreted into media by BMDMs stimulated with LPS was measured by ELISA. Aortic athero was compared among 2 cohorts of C57BL/B6-congenic Apoe−/− mice: (1) LysM-Cre+/+ Kalrn flox/+ (“Mφ-Kalrn−/+”) and (2) Kalrn flox/+ (control). Mice were matched for age and sex, and fed a Western diet for 12 weeks from the age of 4 weeks. Cholesteryl ester content of atherosclerotic plaques was visualized using Sudan IV dye and aortic athero was quantitated in a manner blinded to specimen identity (ImageJ).

Results: When compared with WT Mφs, Kalrn−/− Mφs had 33±9% less LPS-induced Rac1 activation, assessed as by G-LISA (p<0.05). Whereas WT and Kalrn−/− Mφs secreted equivalent amounts of pro-inflammatory IL-6, WT Mφs secreted 40% more anti-inflammatory IL-10 than Kalrn−/− Mφs (p<0.05). Despite these Mφ differences in vitro, in vivo there was equivalent aortic atherosclerosis (assessed en face) in Mφ-Kalrn−/+ and control Apoe−/− mice (n=14 and 11).

Conclusions: We conclude that Kalirin functions as a Rac-GEF in Mφs, and that Kalirin promotes the secretion of IL-10 from Mφs. However, it is unknown at this time if this Kalirin activity has any effect on atherosclerotic plaque development as further studies in mice are pending.
An upright eyedrop bottle: accuracy, usage of excess drops, and contamination compared to a conventional bottle
Isaiah Davies, Ninita Brown, Joanne Wen, Sandra Stinnett, Kelsey Kubelick, Roma Patel, Kristin Benokraitis, Latoya Greene, Curry Cheek, Kelly W. Muir

Background: A staple of standard eye care is the delivery of ocular medications via the standard eyedrop bottle. Despite the ubiquity of the standard eyedrop bottle, patients struggle to properly instill their eyedrops. Proper instillation entails administering one drop into the eye without contaminating the bottle tip. Consequences of improper instillation include the possibilities of under-treatment, over-treatment, systemic side effects, infection, and trauma. In addition to these issues, the standard eyedrop bottle requires that a patient recline their head, a requirement that may be difficult for some patients. The Upright Eyedrop Bottle (UEB) is a novel device that attempts to address many of these issues. This research attempted to determine efficacy of use of the UEB as compared to a conventional eyedrop bottle.

Methods: Experienced eyedrop users were screened for study enrollment by being asked, “Do you ever have trouble getting your eyedrops in?” Patients answering “yes” were eligible for enrollment. Study participants were shown a multimedia presentation regarding proper eyedrop instillation with both a conventional eyedrop bottle and the UEB and were also asked to answer questions regarding their home eyedrop usage. Participants were instructed to instill a single eyedrop in each eye with both a standard bottle and the UEB. They repeated this process three times under direct observation. With each trial the amount of time to instill drops was recorded, as well as whether a drop landed in the eye (accuracy), if excess drops were used, and if the bottle tip was contaminated.

Results: Forty participants were enrolled with an average age of 72.4 ± 8.9 years. The majority of participants were females (24 participants). Thirty four participants had been using eyedrops for at least one year. Sixteen participants had visual acuity worse than 20/40 in both eyes and 9 participants had visual acuity worse than 20/60 in the better eye. The time required to instill eyedrops was less with the UEB in all 3 trials, with the last 2 trials showing statistical significance. There was no difference in accuracy between the conventional bottle and UEB in the left or right eye in any trial. Significantly more participants used excess drops while using the conventional bottle as compared to the UEB across all three trials in both the left and right eye. Participants never contaminated the bottle tip using the UEB. Depending on the trial and the eye, between 42% and 53% of participants contaminated the conventional bottle.

Conclusions: The UEB is a unique device that allows patients to instill their eyedrops without reclining their head. With no difference in accuracy, the UEB was associated with less use of excess drops and less contamination of the bottle tip as compared to a conventional bottle. The UEB has the potential to assist patients with eyedrop placement.
Effects of High-Intensity Interval Training (HIT) in a Hyperoxic-Hyperbaric Environment on Exercise Performance at Altitude
Sophia Dunworth

Background: Recent studies have shown that exposure to nontoxic levels of carbon monoxide can induce skeletal muscle mitochondrial biogenesis. The mechanism by which this occurs is thought to be reactive oxygen species (ROS) signaling. Through a similar mechanism, hyperbaric oxygen (HBO)--which is known to increase ROS--could also induce mitochondrial biogenesis. As the mitochondrial oxidative capacity of skeletal muscle contributes to overall aerobic exercise capacity, HBO-induced changes in mitochondrial biogenesis should enhance exercise performance as measured by maximum oxygen consumption during exercise (VO₂max). In this study, we hypothesized that high-intensity interval training (HIT) while breathing HBO (1) induces mitochondrial biogenesis and therefore (2) is superior at improving exercise performance at altitude when compared to HIT alone.

Methods: After institutional review board approval and informed consent, 21 healthy subjects underwent a vastus lateralis muscle biopsy and a maximum exercise test at 0.56 ATA (simulated altitude of 15,000ft) before and after a HIT training program. Each subject completed six, thirty-minute training sessions over a two-week period. Subjects were randomized to complete training at either 1.4 ATA (a simulated depth of 13 feet of sea water) breathing 100% oxygen (HBO group) or at 1.0 ATA breathing room air (control group). We compared pre- and post-training exercise performance (as measured by VO₂max) for all subjects and for a subgroup of subjects who were more sedentary/recreationally active.

Results: Four subjects were excluded due to equipment errors. The remaining subjects in the control group (n=9) experienced a significant change in VO₂max at altitude following HIT training (pre-training VO₂max=29.00±3.06 (mean±SEM); post-training VO₂max=33.18±2.53; p=0.0337). Subjects in the HBO group (n=8) experienced a similar change in VO₂max at altitude following training, which did not reach statistical significance (pre=31.43±1.50; post=35.24±1.16; p=0.0658). There was no significant difference between the HBO and control groups with regard to VO₂max (treatment effect=0.37; p=0.8806). Within the subgroup of sedentary/recreationally active subjects, both the control (n=7) and the HBO groups (n=6) experienced a significant change in VO₂max at altitude following training (Control: pre= 24.83±1.56; post=29.93±1.56; p=0.0053. HBO: pre=29.63±1.24 post=35.27±1.06; p=0.0145). Again, there was no significant difference between the training groups with regard to change in VO₂max following HIT training (treatment effect=-0.53, p=0.7861).

Conclusions: We conclude that exercise training with hyperbaric oxygen is similar to exercise training alone for improving VO₂max at altitude. Despite the lack of physiological differences between training techniques, HBO may still induce muscle mitochondrial biogenesis. Vastus lateralis muscle biopsy results are pending.
Real-time continuous monitoring of subcutaneous tissue oxygenation
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Background: This study aims to supplement diagnostic fluorophore injection with continuous oxygen monitoring for determination of critically ischemic flap regions. Currently, a single intraoperative injection of a fluorophore into the bloodstream is used to indicate tissues that have subjectively adequate perfusion. We used novel implantable oxygen biosensors to validate a system that continuously reports tissue oxygenation.

Methods: Three of these sensors were injected along the length of a caudally based McFarlane flap and one in the right upper limb. These sensors contain a porphyrin dye whose fluorescence and phosphorescence lifetime change with oxygen concentration. Tissue was challenged during hyperoxia (100%) and normoxia (21%) for 5 minutes each and the difference in tissue oxygen tension was compared.

Results: On day 3, the cranial aspect of the flap had the greatest decrease in tissue oxygen tension (p=0.03) compared to the caudal aspect. Blinded observers indicated adequate perfusion along the entire flap on day 3 according to sodium fluorescein injection. On days 7 and 14, the cranial aspect of the flap underwent necrosis. The oxygen sensors were able to identify critically ischemic flap regions on day 3, four days earlier than sodium fluorescein injection.

Conclusions: These sensors temporally tracked tissue oxygenation and predicted regions of the flap that would undergo necrosis. Clinical application of these sensors offers a quantitative method of assessing tissue viability. These sensors could dramatically improve outcome for patients requiring tissue oxygen monitoring and help inform physicians’ treatment plans earlier than current standards.
Bone marrow entrapment as a novel form of T cell dysfunction in patients and mice with glioblastoma

Harrison Farber

Background: Glioblastoma (GBM) is the most common and deadly adult primary malignant brain tumor. Its median overall survival of less than 15 months underscores the need for novel treatments. Although immunotherapy has emerged as a promising candidate, efficacy has been limited due, in large part, to the excessive immunosuppressive nature of these tumors. Observed immune deficits include severe reductions in systemic T cell number and function. In the present study, we sought to characterize GBM-induced immune deficits in the T cell compartment.

Methods: Various clinical and pre-clinical studies were undertaken to complete this work. IRB approval was obtained for all clinical studies. *In vivo* pre-clinical experiments were conducted using syngeneic and orthotopic intracranial murine models of glioma, metastatic melanoma, breast, and lung cancer. Harvested tissues included blood, spleen, cervical lymph nodes, thymus, and bone marrow (BM). Tissues were processed into single cell suspensions, labeled with antibodies, and analyzed by flow cytometry. For studies requiring adoptive cellular transfer, cells were harvested from donor mice, labeled with CFSE *ex vivo*, and injected via tail vein into recipient mice.

Results: A retrospective review of 284 GBM patients revealed significant lymphopenia. Patients simultaneously exhibited lymphoid organ retraction, averaging a 30% reduction in splenic volume. These findings were recapitulated in multiple models of murine GBM, where mice exhibited a global reduction in both CD4 and CD8 T cell compartments. Naïve, rather than memory, T cells were more profoundly affected. In assessing other immune elements in these models, we found retraction of secondary lymphoid organs (SLOs), but contrarily, an expansion of T cell number in the BM. This finding prompted the prospective collection of blood and BM from patients with GBM and normal controls, which likewise revealed increased numbers of naïve T cells in the BM of these patients. Using various murine models of intracranial glioma and brain metastases, we show that this phenomenon is specific to the intracranial microenvironment. Adoptive cell transfer experiments reveal that this finding is mediated by intrinsic changes to T cells themselves, rather than to the BM, and that these cells become sequestered within the BM rather than direct homing. While factors mediating entrance and egress of T cells in the BM are relatively unknown, the sphingosine-1-phosphate receptor type 1 (S1P1)-S1P axis has been shown to mediate T cell egress from the BM in the pathologic state of alymphoplasia in which mice display SLO retraction. Given the phenotypic similarity to our murine GBM models, we investigated this axis and found that downregulation of S1P1 expression on the surface of T cells in GBM-bearing mice precludes their responsiveness to blood-borne S1P, thus leading to their sequestration in the BM. Additionally, stabilization of S1P1 on the T cell surface using transgenic mice abrogated this phenomenon. T cell remobilization alone provided a survival benefit in murine GBM with accompanying increased numbers of activated tumor-infiltrating lymphocytes.

Conclusions: We, therefore, advance here a novel mode of T cell dysfunction in cancer that is specific to the intracranial environment: S1P1-mediated BM T cell sequestration. Importantly, these data compel a deeper understanding of the mechanisms that lead to brain tumor-induced S1P1 downregulation, and reveal new therapeutic targets aimed at reversing T cell compartmentalization within the BM, thus allowing these cells to return to the circulation to serve as the substrate for enhanced anti-tumor responses. Importantly, these observations have significant implications for the booming field of immunotherapy, as T cell remobilization may be requisite for strategies that have succeeded in other cancers but have been limited in efficacy against GBM.
Majority of Patients Seek Medical Care Shortly Prior to an Out of Hospital Cardiac Arrest
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Background: Sudden cardiac arrest causes over 300,000 deaths each year in the United States and accounts for over half of all cardiac-related mortality. Many clinical traits have been identified, such as a low ejection fraction, which indicate when a patient may be at an increased risk for Sudden Cardiac Death (SCD). However, the majority of patients with SCD have no previously identified risk factors. We utilized the robust patient records of Durham County EMS and Duke University Health System to analyze any pre-arrest clinical data that may direct future risk stratification.

Methods: All subjects with Out of Hospital Cardiac Arrest (OHCA) as identified by Durham County EMS in Durham County, NC from 1/1/2008-12/31/2014 were included for analysis. OHCAs were defined by emergency medical services, and a cardiac etiology was verified via two-physician chart review. Patient identifiers were linked with data from Duke University Health System, the largest provider of healthcare in Durham County. Baseline characteristics were imported from healthcare system databases. Chart review identified the primary diagnosis code for the most recent healthcare encounter, defined as a physician visit, prior to arrest, and a correlating ICD-9 code was identified. Comparisons were made among groups using univariate analysis and survival to hospital discharge was compared among groups using logistic regression models.

Results: There were 951 cases of OHCA during the study period and 810 (85.2%) of these patients had been seen previously in the Duke Health System. Among them, 653 (80.6%) had a physician-verified OHCA, and 567 patients had a prior physician encounter on record. These encounters occurred within 7 days of OHCA for 138 (21.1%) of patients, and within 30 days of OHCA for 321 (56.6%) patients. Among all visits, the majority of physician encounters were in an ambulatory clinic (54.3%), and were most frequently for a visit diagnosis related to infections (18.3%), pain (14.5%), or a cardiac complaint or condition (12.7%). Patients seen by a physician within any timeframe prior to their arrest were less likely to survive to hospital discharge (≤7 days: OR 0.214, CI 0.73-0.632; 8-60 days: OR 0.376, CI 0.148-0.956; >60 days: OR 0.322, CI 0.138-0.752).

Conclusion: Patients are likely to have been seen by a physician shortly prior to their OHCA. These physician visits were frequently for infectious, cardiac, and pain-related etiologies, and physician visits were associated with decreased survival to hospital discharge. Further analysis of the pre-arrest physician encounters may improve risk stratification for OHCA.
Background: Preterm birth is the leading cause of neonatal morbidity and mortality, but has been difficult to mitigate, as it represents the common undesired endpoint of many different biologic processes. One such etiology is inflammation stimulated by the allogeneic mismatch between mother and fetus, similar to transplant rejection. Although there are many known mechanisms for maintaining immune tolerance in pregnancy, inappropriate activation of inflammation often underlies pathologic processes. The hallmark of allogeneic rejection is infiltration of T cells into the grafted tissue. In pregnancy, lymphocytic infiltration of the placenta on histology is called “chronic placental inflammation,” and includes maternal T cell infiltration of the placenta. CXCR3 is a receptor expressed on Th1 T cells that has been shown to be the key leukocyte trafficking receptor in organ transplant rejection. Given biologic similarities between pregnancy and organ transplantation, we hypothesized that CXCR3 plays a critical role in chronic placental inflammation in preterm birth. We investigated the levels of CXCR3 expression in preterm placentas with histologic evidence of chronic placental inflammatory lesions, as well as CXCR3 levels between different clinical presentations of preterm birth.

Methods: Placentas from 56 singleton births between 23 weeks and 33 and 6/7 weeks gestation were collected, formalin fixed, and paraffin for clinical evaluation. Placental slides were examined by pathologist RB for diagnosis of chronic inflammatory lesions. Separate placental slides were stained for CXCR3 expression using immunohistochemistry after optimization of experimental conditions. Stained slides were digitally scanned, then amount of CXCR3 staining was quantified as the ratio of stained area to total tissue area using Adobe Photoshop software. Wilcoxon rank sum and Fisher’s exact test were used to analyze variables between each comparison group. Subjects were grouped either by histology diagnosis or by clinical presentation (indication for delivery). Multiple linear regression models were used to test these effects on CXCR3 while controlling for preterm labor and acute chorioamnionitis. P<0.05 was considered statistically significant.

Results: In our cohort, 44 patients had evidence of chronic placental inflammation while 12 did not. In terms of clinical presentation, 21 patients had spontaneous preterm delivery, while 35 had a medically-indicated preterm delivery. CXCR3 expression was significantly lower in patients with evidence of chronic placental inflammation when compared to those without chronic placental inflammation after controlling for preterm labor and acute chorioamnionitis (-9.65; 95% CI = -18.03, -1.28; P = 0.03). There was no evidence of association between CXCR3 and indication for delivery after controlling for preterm labor and acute chorioamnionitis (-9.85; 95% CI = -21.81, 2.11; P = 0.11).

Conclusions: Our results demonstrate significant variation in CXCR3 expression on placental histology from preterm birth placentas. However, these results do not support the hypothesis that CXCR3 is the primary lymphocyte trafficking receptor in chronic placental inflammation. This finding suggests a functional role for CXCR3 in placental inflammation among phenotypes of preterm birth which require more specific characterization.
Comparing health outcomes and primary care physician utilization among low-income adults with type 2 diabetes and/or hypertension receiving either standard or intensive care management
Javier Galán

Background: Care management programs aim to improve individual health outcomes by using care managers to assist with the integration of heterogeneous health care and social service components. The Project Access of Durham County (PADC) and Local Access to Coordinated Healthcare (LATCH) organizations administer a care management program to an uninsured and racially diverse population in Durham, North Carolina. This population experiences substantial disparities in type 2 diabetes and hypertension prevalence and secondary complications. PADC-LATCH administers this program through standard (SCM) and intensive (ICM) protocols. The intensive protocol consists of more frequent and comprehensive individual encounters and is reserved for individuals meeting specific criteria with respect to chronic disease diagnoses and/or uncontrolled chronic disease. This evaluation compares the effect of each protocol on clinical outcomes, PCP utilization, and care management goal achievement.

Methods: Individuals having a recorded diagnosis of type 2 diabetes and/or hypertension and who were enrolled and receiving care management under the SCM (n=123) or ICM (n=23) protocols between January 1, 2015 and June 30, 2015 were considered in the final evaluation. Individual data were obtained through analysis of care management notes and medical records. A secondary data analysis was performed to investigate outcome changes within and across each group.

Results: Those enrolled in ICM experienced a reduction in HbA1c from 10.6 to 9.51% (P=0.1), an 8.76% decrease, compared to individuals in SCM who had a small increase in HbA1c from 6.73 to 6.78% (P=0.92), a 2.03% increase. The difference in percent change in HbA1c across groups was not statistically significant (P=0.09). Both groups saw non-significant reductions in both systolic (ICM: 141.6 ± 19.1 to 137.2 ± 18.6, P=0.17 and SCM: 143.5 ± 21.2 to 140.6 ± 18.9, P=0.19) and diastolic blood pressure values (ICM: 81.5 ± 11.2 to 79.8 ± 12.1, P=0.60 and SCM: 85.8 ± 10.8 to 84.5 ± 10.6, P=0.23). There was no statistically significant difference in percent change in systolic (P=0.46) and diastolic blood pressure values (P=0.99) across groups. Those receiving SCM had a statistically significant reduction in PCP visits of 16.7% (P<0.05) compared to a 0.8% (P=0.25) reduction among individuals receiving ICM, with no significant difference between groups (P=0.39). Lastly, only 57.1% of ICM individuals achieved their care management goals compared to 78.2% of those enrolled in SCM (P<0.05).

Conclusions: SCM and ICM protocols have varying results on outcomes of interest. Those enrolled in SCM saw a decrease in PCP utilization and achieved care management goals at a higher rate than counterparts receiving ICM. Individuals enrolled in the ICM protocol saw decreases only in HbA1c. Effects on blood pressure values were equivocal. This evaluation suggests that ICM is not superior to SCM in achieving desired results, both groups have equivoccal results, and there should be considerations of changing or eliminating both protocols.
A virus, a window, and a gut-brain neurocircuit

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Background: Autism, PTSD, and IBD patients all share one common symptom – visceral hypersensitivity. This symptom occurs when innocuous stimuli, such as nutrients, in the gastrointestinal tract are perceived as painful. Unfortunately, no targeted therapies exist to alleviate visceral hypersensitivity and, worse, the neural circuits underlying visceral sensation are poorly described further precluding the development of therapies. Here, we discovered a physical connection between sensory enteroendocrine cells of the colon and vagal neurons. The neural circuit was revealed using a monosynaptic rabies virus. We then develop two methods to study the cells in the circuit in the living mouse.

Methods: We used three methods:
1. A mutant rabies virus that can only spread one synaptic connection. The virus is known as EnvA B19G SADG-GFP rabies and lacks a glycoprotein necessary for synaptic spread. We also developed a transgenic mouse that expresses the glycoprotein in enteroendocrine cells. When delivered by enema, the rabies virus infects enteroendocrine cells and spreads onto vagal nodose neurons, revealing a physical path from the surface of the colon to the vagus nerve.
2. An imaging platform for the vagal nodose in vivo. Using a microinjector system, we infected the vagal nodose with a viral vector carrying a calcium reporter, AAV5-GCaMP6s. Five weeks later, the nodose ganglion was exposed by surgery, mounted on a coverslip, and imaged using two-photon microscopy.
3. An abdominal window implant to record enteroendocrine cells in vivo. We developed a transgenic mouse in which enteroendocrine cells express the calcium reporter GCaMP6s. The mice were implanted with an abdominal window and enteroendocrine cell activity recorded using two-photon microscopy in the living mouse.

Results: By using a mutant rabies virus, we revealed a novel neural circuit between colonic enteroendocrine cells and vagal nodose neurons. We then optimized two imaging methods to study the vagal nodose ganglia and sensory enteroendocrine cells in vivo.

Conclusions: Our preliminary results indicate that enteroendocrine cells are continuously active, even in the absence of stimuli. This is a trait shared with other sensory epithelial cells and can only be observed in vivo in the intact animal. These methods open the possibility to study visceral sensitivity in vivo, and can lead the way to creating treatments for visceral hypersensitivity.
Interfrontal Angle in the Measurement of Outcome and Relapse in Metopic Craniosynostosis: Utility and Limitations

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Background: Recent progress has been made in diagnosing and treating metopic craniosynostosis; however we do not fully understand the post-surgical relapse that occurs. The purpose of this retrospective study was to utilize a previously validated measurement – the interfrontal angle (IFA) – as a means to objectively quantify the rate and pattern of postsurgical relapse, while also attempting to elucidate the variables that can predict its occurrence and severity.

Methods: Patients with surgically treated metopic craniosynostosis at a single institution were identified, and those who had low-dose CT scans preoperatively, immediate postoperatively (~POD 3), and delayed postoperatively (~1 year) were isolated (n=19). The IFA from each scan was measured using software to create three-dimensional reconstructions, and the corresponding relapse was calculated. Relapse was defined as the percent of the surgically induced change in IFA that was retained after the first postoperative year.

Results: The mean IFA’s at the preoperative, immediate postoperative, and delayed postoperative time points were: 119.3° (SD 9.8), 139.6° (SD 6.3), and 135.3° (SD 7.1), respectively. The average change in IFA from the preoperative to immediate postoperative period was 20.4°, attesting to the corrective ability of anterior cranial vault remodeling. Overall, the average relapse was $\bar{\xi} = 0.79$; this translates to retention of 79% of initial surgical change after the first postoperative year. Fourteen out of nineteen patients (73.7%) experienced relapse with an average of $\bar{\xi}_{Relapse} = 0.624$. A model found that using both increasing severity of preoperative disease and increasing age at surgical intervention correlates with an increased occurrence of relapse (p=0.011), but independently, neither were significant predictors (p-values of 0.127 and 0.191, respectively). Additionally, simple linear regression was used to create a model that utilizes preoperative IFA to predict the change in IFA that would accompany anterior cranial vault reconstruction (p<0.0001).

Conclusions: This study demonstrates the ability of the IFA to objectively quantify the postsurgical relapse that occurs within the frontal bandeau. The extent of this relapse appears to occur without relationship to individual predictors such as race, age at intervention, and preoperative severity. However, due to the confines of its anatomical location, the IFA cannot be used to describe the holistic relapse that occurs and therefore cannot predict long-term outcomes. The IFA extends itself as a valuable research tool by providing surgeons an objective model to predict surgical impact based upon preoperative severity on a case-by-case basis.
Lifestyle Factors and Health-Related Quality of Life in Bladder Cancer Survivors: A Cross-Sectional Study
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Background: Diet and physical activity are two modifiable factors that have been shown to significantly improve health-related quality of life (HRQOL) in a variety of cancer patients. However, little is known about the dietary and physical activity patterns of bladder cancer survivors and how these are related to HRQOL in the United States. Our objective was to describe HRQOL, self-reported physical activity, and dietary patterns and examine the associations between these measures in a large cohort of bladder cancer survivors.

Methods: Bladder cancer survivors identified through an institutional database were mailed a survey that included the Functional Assessment of Cancer Therapy Bladder Cancer (FACT-BI), the International Physical Activity Questionnaire (IPAQ-L), and the Diet History Questionnaire II (DHQ2). The FACT-BI is a validated 39-item questionnaire designed to measure the quality of life of patients treated for bladder cancer. The IPAQ-L is a well studied and validated 27-item questionnaire designed to quantify a patient’s physical activity. The DHQ2 is a validated 151-item food frequency questionnaire recommended by the National Cancer Institute. To measure diet quality, a Healthy Eating Index-2010 (HEI) total score and component scores were calculated for each subject based on DHQ2 results. Comorbidities, smoking status, BMI, and cancer-related details were abstracted from subjects’ electronic medical records. Multiple regression models were used to evaluate associations between HRQOL and physical activity and diet quality. The analyses were repeated using multivariate ordinal logistic regression to control for relevant covariates, including age, gender, cancer grade, cancer stage, presence of comorbidities, and surgery type (radical cystectomy or TURBT).

Results: Out of 962 subjects who received the survey, 472 (49%) responded. The mean age was 74 years, 81% were male, and 87% were Caucasian. Respondents performed a median of 2794 MET-min/week of total physical activity, 198 MET-min of transportation-related physical activity, 720 MET-min of domestic physical activity, 330 MET-min of recreational physical activity, and 0 MET-minutes of job-related physical activity. The ranges for dietary macronutrients and micronutrients provided by the USDA were used to determine the percentage of respondents who met guidelines. The mean ± standard deviation HEI-2010 total score was 65.9 ± 10.7, compared to the US population mean of 49.9 ± 0.5. For individual food groups and nutrients, there was particularly poor adherence to whole grains, dairy, fatty acids, and sodium guidelines. Both physical activity and diet quality were positively associated with health-related quality of life, even after adjusting for relevant clinicodemographic covariates.

Conclusions: This large contemporary cohort of bladder cancer survivors reported high levels of physical activity and moderate adherence to the USDA Dietary Guidelines. Physical activity and diet quality were both positively associated with HRQOL. Further studies investigating the causal relationship between HRQOL and diet and physical activity in the post-treatment setting in bladder cancer survivors are warranted.
Response to Respiratory Syncytial Virus (RSV) Infection during Prostaglandin-Endoperoxide Synthase 2 (Ptgs2) Gene Knockdown: An In Vivo and In Vitro Analysis

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Background: RSV is a single-stranded RNA virus of the Paramyxoviridae family that is the leading cause of hospitalizations for infants worldwide. It is the major cause of bronchiolitis. While the majority of children will have cold-like symptoms, others will require hospital admission or will die due to respiratory insufficiency. Previous studies have shown that there is most likely a genetic susceptibility to RSV infection and severity. A GWAS analysis in inbred strains of mice identified prostaglandin-endoperoxide synthase 2 (Ptgs2, aka COX-2) as a potential candidate gene for differential susceptibility to RSV disease. PTGS2 expression has also been shown to be upregulated during RSV infection and to participate in immune response in humans post viral infection.

Methods: Mice with targeted deletion of Ptgs2 (Ptgs2−/−) and wild-type (Ptgs2+/+) mice were infected intranasally with RSV or vehicle (control). On post-infection (PI) days 1 or 4, the mice were killed and bronchoalveolar lavage (BAL) was performed on the left lung. Differential counts were performed on the cells recovered in BAL fluid to evaluate lung inflammation. For the in vitro experiment, Ptgs2 was knocked down in A549 and BEAS-2B human lung epithelial cell lines using a lentiviral system and celecoxib, a Ptgs2 (COX-2) synthase inhibitor. RNA was isolated 48 hours after infection, and mRNA expression of genes that regulate immune response and antiviral response were analyzed.

Results and Conclusions: Mean numbers of total BAL cells were significantly (P < 0.05) increased in Ptgs2+/+ and Ptgs2−/− mice 1 and 4 days PI compared to vehicle control mice. However, mean BAL cell counts were significantly greater in Ptgs2−/− mice compared to Ptgs2+/+ mice on both days. Similarly, mean numbers of BAL neutrophils (1 day PI) and lymphocytes (4 days PI) were significantly increased in both genotypes, but were significantly greater in Ptgs2−/− mice compared to Ptgs2+/+ mice. In vitro, we achieved greater than 50% knockdown of Ptgs2 mRNA expression in the A549 and BEAS-2B polyclonal cell lines. A monoclonal cell line of each is being derived, and further analysis with RSV infection will be performed on these lines. Celecoxib (30 uM) significantly inhibited RSV-induced increases in IL8 and IL6 compared to DMSO controls in both cell lines. Results of the in vivo and in vitro studies are consistent with the GWAS findings that Ptgs2 is determinant of susceptibility to RSV disease and may have intervention implications to alleviate RSV disease phenotypes.
Cytokine Receptor Knockdown via CRISPR/Cas9 for Treatment of Disc Herniation-Associated Pain

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Background: Intervertebral disc (IVD) disorders contribute to pain and disability in up to 80% of the US population. IVD herniation is frequently associated with radicular pain mediated by both mechanical compression of nerve roots and the presence of multiple proinflammatory cytokines (e.g. TNF-α, IL17A). Previously, biologics have been explored to antagonise these cytokines with application to neuroinflammation and symptom development. Recent advances in the use of the novel genome engineering tool Clustered Regularly Interspaced Short Palindromic Repeats interference (CRISPRi) enable highly specific knockdown of target proteins using guide RNAs (gRNA) directed to loci of interest.

Methods: We developed CRISPRi-gRNA constructs to knockdown receptors to TNF-α and IL17 to abrogate development of neuropathic pain. Guide RNA sequences targeting rat TNF receptor type I (TNFRI) and IL17 receptor type A (IL17RA) promoter regions were selected based on appropriate protospacer adjacent motifs (crispr.mit.edu), cloned into plasmids under control of the U6 promoter, and screened for effective knockdown via qRT-PCR. The gRNA showing greatest knockdown was cloned into lentiviral (LV) vectors to facilitate single-vector co-expression with dCas9-KRAB-GFP. Rat PC12 neuroendocrine cells and primary DRG neurons were then transduced with TNFRI and IL17RA LV CRISPRi vectors and qRT-PCR was performed to identify knockdown. Transduction efficiency was measured via flow-cytometry for GFP expression (Accuri C6). Functional effect was confirmed by quantifying TNF-α- and IL17A-induced ERK phosphorylation in cell isolates (PerkinElmer AlphaLISA).

Results: Selected CRISPRi-gRNA constructs were able to knockdown 78% and 95% of mRNA for TNFRI and IL17RA, respectively, in rat PC12 cells. Flow cytometry in primary rat DRG cells demonstrated 60.3% transduction efficiency. Phosphorylated ERK levels significantly decreased in response to TNF-α challenge after both TNFRI (by 77%) and IL17RA (by 67%) CRISPRi knockdown in PC12 cells (figure). This suggests that CRISPRi technology has the ability to interfere with TNF-α-induced cell signalling that can contribute to painful neuropathy.

Conclusions: CRISPRi knockdown of TNFRI and IL17RA can be used to modulate cellular response to inflammatory challenges in neuronal cells, DRG neurons and cells. Despite incomplete transduction efficiency, knockdown of either receptor expression inhibits ERK, a proximal effector in the intracellular signalling pathway associated with pain development. Future work will evaluate functional assessments of CRISPRi-mediated knockdown in DRGs in vitro and in vivo following cytokine challenge or IVD herniation. CRISPRi technology offers a novel therapeutic means for delivering targeted reduction of the inflammatory environment associated with disease.
Understanding the Characteristics of Primary Care Patients with Frequent Emergency Department Use

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Background: Patients with high rates of emergency department and hospital use have become an important focus in population health efforts because of the potential to reduce costs while improving quality of care. The mixed results from various care management interventions suggest an inadequate understanding of patient needs and the factors that drive high utilization. This study seeks to understand the underlying drivers behind frequent ED use among patients enrolled in primary care in order to identify unmet medical and psychosocial needs for these patients.

Methods: Patients enrolled at an academically-affiliated general internal medicine clinic were categorized according to ED utilization during a 12-month period (July 1, 2014 to June 30, 2015): non-utilizers (0 ED visits, n=2441), non-high utilizers (1-4 ED visits, n=1386), and high utilizers (n≥5, n=260). For all ED visits during the same period (n=4776), the leading chief complaints, admission rates by complaint, and average number of repeat visits for the same complaint were analyzed for high utilizers and non-high utilizers. Number of complaints per patient and average time between return ED visits for the same complaint were also assessed. Ten of the highest utilizers from each of the 3 leading chief complaints (n=30) received an in-depth chart review to assess the documented themes that underlay patterns of repeated ED use for the same complaints.

Results: High utilizers demonstrated a much higher burden of chronic disease, mental illness, and substance abuse than non-utilizers and non-high utilizers. However, the presenting chief complaints of high utilizers were statistically similar to non-high utilizers. High utilizers were less likely to be admitted to the hospital (21% vs 26%, p<0.001) and more likely to present repeatedly for the same chief complaints (mean repeat visits 2.4 vs 1.2). Certain complaints, such as shortness of breath (mean 5.1) and seizures (mean 5.0), repeated more frequently than other complaints. Over 85% of high utilizers had ≥4 unique chief complaints. Most ED visits for high utilizers clustered together temporally, with 55% of repeat visits occurring less than 30 days apart (median of 20 days between visits, IQR: 38). Time between repeat visits varied by chief complaint, with psychiatric visits demonstrating the shortest time to repeat visit (median 17.5 days, IQR: 39.5). Abdominal pain, chest pain, and shortness of breath were the leading chief complaints overall, leading causes of admissions, and leading causes of repeat visits among high utilizers. Chart review revealed that repeated visits for these 3 chief complaints were often associated with a wide range of chronic conditions confounded by substance abuse, anxiety, and treatment non-adherence.

Conclusion: The reasons for high ED utilization are a complex mix of concomitant chronic disease, mental illness, and social factors, which create patterns of repeated visits for the same complaints. Most high utilizers, however, have many reasons for visiting the ED, making future utilization difficult to predict. More research is needed to understand in greater depth the behavioral and psychosocial factors that play a role in high ED utilization.
Can BI-RADS features on mammography be used as a surrogate for expensive genomic testing in breast cancer patients?

Michael Harowicz, Maciej Mazurowski, PhD

Background: Physicians rely on expensive genomic analysis of tumor sample as the standard of care for the workup of invasive breast cancer. Breast cancer is grouped by molecular subtype, each of which has its own behavioral pattern of tumor presentation, likelihood of metastatic spread, and response to chemotherapy and radiation. The subtype data is a necessary part of the formula physicians use to devise an appropriate treatment strategy. In recent years there has been a rapid increase in the number of genomic tests available that provide even more detailed data, one of which is the Oncotype DX test, which is currently included in the National Comprehensive Cancer Network and the American Society for Clinical Oncology guidelines for early breast cancer. This 21-gene analysis is used on a subset of patients to calculate an Oncotype DX recurrence score (ODRS), which corresponds to the risk of breast cancer recurrence. The ODRS is a beneficial tool when used alongside other factors to potentially spare early stage estrogen receptor positive invasive breast cancer patients with a low ODRS chemotherapy and its side effects. However, the test comes at a $4,000 cost. Radiogenomics, a novel field that investigates the relationship between imaging phenotypes and genomic characteristics, may offer a less expensive and less invasive surrogate for the molecular subtype and ODRS by using data already available to physicians. National guidelines recommend screening mammograms for breast cancer, and abnormal lesions are re-imaged using a diagnostic mammogram meaning that many women diagnosed with breast cancer have already had a mammogram performed. The radiologist reading the mammogram provides a descriptor of a lesion’s shape and margin using the Breast Imaging-Reporting and Data System (BI-RADS). This study focuses on the relationship of these BI-RADS features with molecular subtype and ODRS respectively.

Methods: A retrospective chart review of 304 women with a pathologic diagnosis of invasive breast cancer between September 2007 and June 2009 was performed. Clinical data, pathologic tumor data, and BI-RADS tumor descriptors of shape and margin from the radiology report of a preoperative mammogram were collected. The final cohort included patients with a mammography BI-RADS feature (shape or margin) and a genomic feature (subtype or ODRS), which resulted in the following: shape vs. subtype (n=69), margin vs. subtype (n=78), shape vs. ODRS (n=20), and margin vs. ODRS (n=18).

Results: A Fisher’s exact test was used to examine the relationship between the given BI-RADS feature and the genomic feature. For the analysis the ODRS was grouped into 1 of 3 categories: <18 (low risk), 18-30 (intermediate risk), or >31 (high risk). The p-values are the following: shape vs. subtype (p=0.0171), margin vs. subtype (p=0.1072), shape vs. ODRS (p=0.7839), and margin vs. ODRS (p=0.6047).

Conclusions: These preliminary findings suggest that an imaging-based surrogate for molecular subtype using BI-RADS shape features on mammography may be a valid and less expensive alternative to genomic testing. The association between BI-RADS features and ODRS was not found to be significant, although this aspect of the study was limited by a small sample size.
New Prognostic Grade Group (PGG) Prostate Cancer Grading System: Can multiparametric MRI (mpMRI) and TRUS-guided biopsy accurately separate patients with low, intermediate, and high grade cancer?

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Background: Prostate cancer (PCa) is the most common noncutaneous malignancy in men, but some forms of this disease are more aggressive than others. Patients with less aggressive disease may be appropriate for less invasive treatment, such as active surveillance, while men with high risk PCa need definitive treatment, such as radical prostatectomy (RP). Prostate cancer has traditionally been diagnosed by systematic transrectal ultrasound-guided (TRUS-G) biopsy, but recently, multiparametric MRI (mpMRI) has emerged as a powerful tool in the detection and staging of PCa. The new Prognostic Grade Group (PGG) system reflects the generally indolent nature of Gleason 3+3=6 PCa compared to disease with predominant Gleason 4 components. This underscores the need to accurately separate disease into low (Gleason 3+3=6) and high grade (Gleason 4 or 5 predominant), and potentially also into intermediate grade (Gleason 4 present but not predominant) categories. We aim to determine accuracy of mpMRI and transrectal ultrasound-guided systematic biopsies in predicting pathologic grade of index lesions after RP using the new PGG PCa grading criteria.

Methods: In this retrospective, HIPAA-compliant, IRB-approved study, 157 patients with PCa who underwent 3 Tesla mpMRI with endorectal coil and TRUS-G biopsy before RP were included. MpMRI was used to classify index lesions using a two-tier (low grade/PGG 1 vs. high grade/PGG 2-5 PCa) or a three-tier system (low grade/PGG 1 vs. intermediate/PGG 2 vs. high grade/PGG 3-5 PCa) using a combination of qualitative and quantitative metrics. The accuracy of mpMRI and pre-RP TRUS-G biopsy were compared against RP for each classification system.

Results: The predictive accuracy of mpMRI and TRUS-G biopsy using the two-tier system is higher (0.78 & 0.83, respectively) than when using the three-tier system (0.45 & 0.62, respectively). Using a three-tier system, there were similar rates of undergrading between mpMRI and TRUS-G biopsy compared to RP (16% & 19%; respectively); rate of overgrading of disease was higher for mpMRI versus TRUS-G biopsy compared to RP (39% & 19%, respectively). When mpMRI and TRUS-G biopsy are used in conjunction, rate of undergrading is 6% and overgrading is 11%.

Conclusions: The accuracy of TRUS-G biopsy is lower using a three-tier system versus a two-tier system. The same is true for mpMRI but to a greater extent. TRUS-G biopsy tended to undergrade lesions, while mpMRI tended to overgrade lesions. Rates of under- and overgrading decreased when both techniques were combined, suggesting these two modalities may be complementary in accurately predicting tumor grade and thus determining the most appropriate treatment strategy. MpMRI has high accuracy with low vs. high grade PCa but work is needed to define criteria of intermediate grade PCa and to optimize PCa grading using new PGG criteria.
Three-dimensional nanostructure of the tuft cell
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Background: Whether one calls them peculiar, caveolated, or tuft cells, these are mysterious cells in the epithelia of humans and animals. Recognized by a microvilli tussock, the tuft cell was first classified as a distinct epithelial cell lineage in the gut. They are associated with neoplastic transformations, crypt cell differentiation, and chemosensation. Recent studies have demonstrated a critical role for tuft cells in coordinating the immune response to parasitic infection. Nonetheless, the mechanism behind each of these actions remains cryptic.

Methods: We reasoned that function could be derived from a complete account of the tuft cell ultrastructure at nanometer resolution. We approached the problem with two vanguard electron microscopy techniques: Automatic Tape-collecting Ultra-Microtome (ATUM) and serial block face (SBEM) scanning electron microscopies. ATUM and SBEM are both technologies that allow for automated serial sectioning and reconstruction of tissue ultrastructure in three dimensions. Tuft cells were identified by fluorescence in the colonic epithelium of transgenic ChAT-eGFP mice using confocal microscopy. The confocal data was correlated with 300µm x 300µm low-resolution SEM survey images to identify cells of interest. These were reimaged at a final resolution of 4nm/pixel for ATUM and 7nm/pixel for SBEM, which was sufficient to identify organelles and secretory vesicles. We then processed and rendered the complete ultrastructure of three tuft cells in 3D.

Results: At high resolution, the conspicuous microvilli tuft confirmed the identity of the cells located by fluorescence. Starting at the cells’ base, our results exposed a short (~5µm) basal cytoplasmic process, which contained no vesicles and contacted no neurons. Around the cell periphery, several thin (~1 µm) cytoplasmic spinules were observed. The cytospinules protruded into the cytoplasm of adjacent epithelial cells and made invaginations into their nuclear envelope. Finally, reconstruction revealed an elegant network of interconnected tubules, which extended from cytosolic caves at the base of the microvilli. The tubules penetrated several microns into the cell, merged into the rough endoplasmic reticulum, and therefore produced an unbroken continuity between the rough ER and gut lumen. From the cytosolic side, the tubules were associated with secretory vesicles. On the luminal side, they were associated with electron dense spheres, known as glycocalceal bodies.

Conclusions: We demonstrated that tuft cells are specifically labeled in ChAT-eGFP mice, making it now possible to investigate tuft cells using a widely available transgenic model. Contrary to previous speculation, no associations between tuft cells and nerves were visible and the basal cytoplasmic process in tuft cells did not contain secretory vesicles. Cytosomal spinules in neurons facilitate the exchange of cytoplasmic cargo between cells. The similar structures in tuft cells may perform a similar function with neighboring nuclei. Finally, previous two-dimensional imaging surveys reported an apical vesicular network, which we instead revealed to be a continuous tubular network. Its microanatomy and location suggest a singular potential for molecular exchange between the tuft cell and the gut lumen, via exoyctic or endocytic mechanisms.
Things That Make People Happy: The Role of Sensory Health, Cognition, and Neural Factors in Older Adults’ Perceptions About Subjective Well-Being


Background: Subjective well-being (SWB) (i.e., happiness, life satisfaction) is a classic construct in gerontology, but the role of patient-level health factors in SWB determinants has not been fully explored. In order to help explain age-related changes in SWB, we sought to understand how aspects of health that commonly deteriorate with age, such as sensory (i.e., vision, hearing) and brain function, relate to variability in self-described contributors to happiness.

Methods: SWB data were drawn from a 60-second verbal fluency task in which 114 seniors (mean age: 74.6 +/- 7.8) were asked to “name things that make people happy.” The 1,731 responses were categorized by a committee of coauthors into 13 domains of SWB through structured content analysis. Vision impairment and hearing impairment were defined by Snellen best-corrected visual acuity and pure-tone audiometry measurements. Cognitive status was assessed with in-person administration of the Brief Test of Adult Cognition by Telephone. Eligible participants (n=57) underwent resting functional magnetic resonance imaging (fMRI) of the brain, which was used to quantify the functional connectivity (FC) of two well-described neural networks with relevance to SWB: 1) the default mode network and 2) between selected regions in the dopaminergic mesocorticolimbic system.

Results: Response patterns elicited by the SWB task differed by gender, sensory status, and cognitive performance. In multiple adjusted analyses, hearing impaired participants listed fewer responses overall (13.59 vs. 17.16; p<0.001). Participants with higher proportions of responses in the “accomplishment” domain (e.g., winning, getting a promotion, earning good grades) had higher FC between the ventral tegmental area and nucleus accumbens, two regions of the mesolimbic network involved in initiating and organizing motivated behavior. Lower FC in the default mode network, implicated in introspection, was observed in those with higher proportions of “social relationship” responses.

Conclusion: Between-person differences in perceived contributors to SWB are related to cognitive and sensory health. Response patterns of hearing-impaired participants in particular suggest that the detrimental effects of this impairment extend into domains of psychological health. Future longitudinal studies and qualitative research are needed to further characterize how age-related declines in vision and hearing may impact contributors to SWB with the ultimate goal of designing programs and services that optimize SWB in seniors coping with sensory losses. Additionally, resting-state functional MRI may be a useful tool for providing new information about neural underpinnings of happiness.
Specialty-based variations in spinal cord stimulation success rates for treatment of chronic pain: Implications towards establishing uniform guidelines for training

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Background: Chronic pain is a major economic concern in the United States resulting in a $635 billion annual cost, with significant functional disability and lost economic productivity. In the past 15 years, a number of randomized controlled trials and meta-analyses have demonstrated spinal cord stimulation (SCS) as a therapeutically beneficial and cost-effective approach to chronic pain management in carefully selected patients. Over the same period, the number of SCS procedures by medical and surgical specialties have grown to service major portions of patients undergoing implantation. Yet trial success rates for SCS remains below 50th nationwide, and predictors of SCS trial outcomes remain poorly understood. The present study examines variations in SCS trial-to-permanent conversion rates based on specialties performing the procedure.

Methods: Thomson Reuters MarketScan database was utilized to obtain a large patient cohort for retrospective analysis. We included all adult patients that underwent a percutaneous or paddle SCS trial with or without internal pulse generator (IPG) implantation from the years 2007 to 2012. Patients were grouped based on a successful conversion of their trial SCS system with a permanent implantation, and divided into categories based on provider type performing the implantation including anesthesiologists, pain medicine specialists, neurosurgeons, orthopedic surgeons, and physical medicine and rehabilitation (PM&R) that perform SCS with frequency (>100 implants). The patient cohort was analyzed using univariate and multivariate models to evaluate for successful conversion between provider types and independent factors influencing the conversion rate.

Results: A total of 7,796 unique instances of SCS implants were identified across 5 providers. Overall, 4899 (62.8%) of those receiving trials underwent permanent SCS system implantation. Anesthesiology performed the majority of implants (32.9%), followed by pain medicine specialists (31.9%), neurosurgery (20.3%), orthopedic surgery (9.8%), and PM&R (5.1%). Compared to anesthesiology, both neurosurgeons (OR 10.07, 95% CI [8.25, 12.29]; p < 0.001) and orthopedic surgeons (OR 4.05, 95% CI [3.30, 4.98]; p < 0.001) had significantly higher conversion rates, while PM&R (OR 0.58, 95% CI [0.47, 0.72]; p < 0.001) had significantly lower. Comparable conversion rates were found between anesthesiologists and pain medicine specialists (OR 0.91, 95% CI [0.81, 1.02]; p = 0.113). Charlson comorbidity scores did not significantly differ among the specialties. Independent factors associated with a higher trial-to-permanent conversion rates included female gender and insurance source.

Conclusions: In this study, we identified a key relationship between the provider performing SCS implantation and subsequent conversion rates. Our results suggest that conversion rates improve when SCS is performed by neurologic or orthopedic surgeons. As the number of SCS implantations continues to increase yearly, our study has important implications for establishing uniform guidelines for training and education of physicians across multiple disciplines.
An Automated Assessment of Speech Patterns in Parents of Preschoolers with Autism Spectrum Disorders Using the Language Environment Analysis (LENA) System
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Background: Atypical language development is one of the hallmarks of Autism Spectrum Disorders (ASD), and child-adult interactions play a critical role in language development. Automated measures are needed to assess language development more efficiently, with less expertise, and in non-clinical settings. The LENA system, consisting of a digital recording device and its accompanying software, captures young children’s language and auditory environment in the home. We examined whether LENA’s parental speech patterns were correlated with validated measures of their child’s communication and social development.

Methods: Twenty-four children with ASD, ages 2-6 years participating in an open-label clinical trial, completed one day of LENA recording at home prior to exposure to the experimental therapy. The LENA software gave several measures of the amount of parental speech, including the number of times an adult spoke and for how long each time (“Adult Segment Duration”), the number of times they started a conversation with their child, and the number of times each conversation went ‘back and forth’ (called “Conversational Turns”) between the child and parent. Participants were assessed in the lab for ASD severity (Autism Diagnostic Observation Schedule-2; ADOS-2); verbal or non-verbal language status (Expressive One Word Picture Vocabulary Test; EOWPVT); and non-verbal IQ (Mullen Scales of Early Learning or the Stanford-Binet Intelligence Scales). Parents reported on their child’s communication and social abilities (Vineland Adaptive Behavior Scale; VABS, and Pervasive Developmental Disorder Behavior Inventory; PDDBI). Linear regressions and two-sample t-tests were used to compare these measures to LENA’s parental speech reports.

Results: The LENA-reported average number of conversational turns per adult-initiated conversation was associated with nonverbal IQ (NVIQ) ($R^2 =0.42$), ADOS total score ($R^2 =0.21$), and most (9/10) of the language and socialization sub-scales of the VABS and PDDBI ($R^2=0.21-0.57$). The strongest association was observed with the VABS Expressive Language V-Scale score ($R^2=0.57$). The mean of this measure also differed significantly by verbal/non-verbal status ($p < 0.01$). LENA’s measure of the proportion of all conversations started by an adult was weakly associated with 6/10 of the VABS/PDDBI subscale scores ($R^2=0.18-0.31$) and NVIQ ($R^2 =0.18$). Average duration of adult speech segments was not associated with any of the VABS/PDDBI measures, the NVIQ, or the ADOS score.

Conclusions: These preliminary findings suggest that, of the parental LENA measures that were assessed, the average number of conversational turns in an adult-initiated conversation is most strongly associated with validated, parent-reported measures of the child’s language and social abilities, as well as with their NVIQ and ASD severity. The average adult segment duration does not appear to be correlated with NVIQ, ASD severity, or parent reports. Our findings support the use of the LENA in a research setting to evaluate language patterns in a natural, home-based environment. Larger confirmatory studies are required.
Mechanisms for Poor Hypertension Control Among Urban African Americans: Examining the Effect of Patient Perceptions on Blood Pressure Self-Management

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Background: Despite the widespread availability of efficacious therapies to treat hypertension, urban African Americans consistently have low rates of hypertension control relative to other groups. Any interventions seeking to correct the significant racial disparities in blood pressure (BP) control must address patient self-management, including patients’ adherence to prescribed medications, capacity to carry out healthy diet and exercise behaviors, and maintenance of medical appointments - a particularly critical mechanism through which patients achieve long-term blood pressure control.

Methods: Data from 159 participants in the Achieving Blood Pressure Control Together (ACT) Study, a randomized controlled trial in Baltimore, Maryland, were used. We assessed patient perceptions of their care, including provider cultural competence and patient-centeredness, using Consumer Assessment of Health Provider and Systems program (CAHPS) surveys. We also assessed self-care behaviors (e.g., diet, exercise, BP monitoring, medication taking, non-smoking) and self-efficacy beliefs (e.g., confidence to engage in self-care behaviors) using the Hypertension Self-Care Profile (SCP). We assessed medication adherence using the Morisky Scale (MMAS). In multivariable logistic regression analyses, we assessed the independent association between patient perceptions of their care with BP self-care, while adjusting for age, gender, poverty status, insurance status, reading grade level, and self-reported diagnosis of diabetes mellitus.

Results: Among study participants, 16% (n=154), 90% (n=158), and 21% (n=149) scored high in the self-care behavior, self-efficacy beliefs, and medication adherence surveys, respectively. After adjustment, patients rating their physicians high in patient provider communication (OR, 3.63; 95% CI, 1.21-10.92), health promotion and education (OR, 3.64; 95% CI, 1.15-11.54), and greater capacity to increase their health literacy (OR, 1.23; 95% CI, 1.01-1.49) had higher odds of engagement in hypertension self-care behaviors. Similarly, patients rating their physicians high in patient provider communication (OR, 2.28; 95% CI, 1.04-5.03) and their capacity to increase their health literacy (OR, 1.11; 95% CI, 1.00-1.23) had higher odds of self-efficacy beliefs around self-care behaviors. Lastly, patients rating their physicians high in patient provider communication had greater odds of medication adherence (OR, 2.61; 95% CI, 1.01-6.73).

Conclusions: African American patients’ self-efficacy beliefs and BP self-care behaviors were strongly associated with perceptions of their providers’ cultural competency (e.g., patient-provider communication, health promotion activity). In addition, patients’ perceptions that providers could bridge gaps in their health literacy were strongly associated with improved self-care behaviors and self-efficacy beliefs. The association between these patient perceptions and self-care management should be further examined in longitudinal studies.
**Ankle-Brachial Index, Symptom Classification, and Perceived Quality of Life in Peripheral Artery Disease**

*Abigail Johnston*

**Background:** The association between ankle brachial index (ABI) values and patients’ perceptions of their health status is poorly characterized. In the PORTRAIT study of patients with intermittent claudication (IC), we compared patients’ ABIs and Rutherford symptom classification with their peripheral artery disease (PAD)-specific health status as measured by the Peripheral Artery Questionnaire (PAQ).

**Methods:** A total of 1,252 patients with new IC or an exacerbation of IC were enrolled at 17 PAD clinics in the United States, the Netherlands, and Australia. Baseline demographic, socio-economic, psychological, and clinical characteristics were recorded from medical records, and patients completed the PAQ. ABI values were categorized as mild (>0.80), moderate (0.40-0.79) and severe (<0.40), and a standard Rutherford symptom classification was utilized. Multivariable linear regression analysis examined the association between ABI and PAQ scores (summary, quality of life [QOL], symptoms, and physical limitations scores) and the association between Rutherford category and PAQ Scores.

**Results:** The median ABI was 0.67; 24.3% had mild, 67.7% PAD, and 8.0% severe PAD by hemodynamic criteria. When compared with patients who had higher ABI values, patients with lower ABI had a higher Rutherford classification and lower PAQ scores. ABI values did not correlate well with PAQ scores (PAQ summary, \( r=0.09, P=0.001 \); PAQ QOL, \( r=0.033, P=0.25 \); PAQ symptoms, \( r=0.044, P=0.12 \); PAQ physical limitations, \( r=0.14, P<0.0001 \)). Rutherford classification had a weak correlation with PAQ scores (PAQ summary, \( r=-0.27, P<0.0001 \); PAQ QOL, \( r=-0.22, P<0.0001 \); PAQ symptoms, \( r=-0.18, P<0.0001 \); PAQ physical limitations, \( r=-0.27, P<0.0001 \)).

**Conclusions:** In a large cohort of patients with IC, there was not a strong association between either ABI values or Rutherford classification with PAD-specific health status. The findings from this study highlight the clinical complexity of PAD and the difficulty in using common hemodynamic and symptom measures to classify the impact of this disease on patients’ health status.
Early Analysis of Laparoscopic Common Bile Duct Exploration Simulation

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Background: Choledocholithiasis has traditionally been managed with laparoscopic cholecystectomy (LC) with either pre- or post-operative endoscopic retrograde cholangiopancreatography (ERCP). Recent literature suggests that a one-step approach of LC with laparoscopic common bile duct exploration (LCBDE) can decrease average length of stay without compromising patient safety or success rate of stone removal when compared to LC+ERCP. However, utilization of LC+LCBDE remains low among practicing surgeons, likely due to limited experience with the LCBDE procedure. We recently developed a LCBDE simulation course for resident surgeons (RS) and practicing surgeons (PS). We hypothesized that course completion would provide the skills necessary to perform LCBDE and would subsequently increase procedure utilization among PS.

Methods: RS and PS were prospectively enrolled in the LCBDE course. Pre-course and post-course knowledge and competency were assessed with a written examination and LCBDE simulation. PS completed a pre-course, post-course, and 1-year follow-up survey to assess course impact and LCBDE comfort (5-point Likert-type scale).

Results: 17 RS and 8 PS were enrolled. All RS were either post-graduate year 3 (PGY-3) or above. Among PS, median years of experience was 6 (IQR 2-12.75) and 88% reported performance of fewer than 5 LCBDE procedures prior to participating in the course. Among all participants, median written test scores improved (70.0% to 80.0%, \( p<0.001 \)) and the median LCBDE simulation time improved (585 seconds to 314 seconds, \( p<0.01 \)). Median written assessment pre-course (70.0% vs 72.5%, \( p=0.953 \)) and post-course (77.5% vs 80.0%, \( p=0.198 \)) scores were not significantly different between RS and PS. Time to simulated LCBDE completion (seconds) improved similarly between groups from pre-course (608.0 vs 521.5, \( p=0.885 \)) to post-course (314.0 vs 373.0, \( p=0.287 \)). PS comfort level with LCBDE improved following course completion (2 to 4, \( p=0.03 \)). On the 1-year post-course survey, all PS reported LCBDE utilization (1 to 6 procedures) and would recommend the course to other surgeons.

Conclusion: This LCBDE course is appropriate for surgical trainees and practicing general surgeons. Both groups demonstrated improvement in knowledge and skills, and PS also report a practice change with increased LCBDE comfort and utilization after course completion.
Evaluating the impact of tumor mutational load on response to immune checkpoint inhibition and radiotherapy in primary mouse models of soft tissue sarcoma
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Background: Preclinical studies using syngeneic tumor models have shown promising results for immune checkpoint inhibitors with and without radiotherapy (RT). However, research with primary tumor models is limited, and syngeneic models using transplanted cell lines may not translate to the clinic. We hypothesize that mutational load is a critical determinant of tumor response to immunotherapy alone, and that RT can improve efficacy of immune checkpoint blockade for tumors with low somatic mutation burden. Here, we test this hypothesis in primary mouse models of soft tissue sarcoma.

Methods: We used two genetically engineered mouse models with Cre recombinase-mediated p53 deletion, either with oncogenic KrasG12D activation (KP) or exposure to the carcinogen MCA (p53fl/fl + MCA), to induce soft tissue sarcomas of the hind limb. Tumor mutational load was assessed by whole exome sequencing. Cohorts in each model received IP injections of isotype control (iso), anti-PD-1, or anti-CTLA-4 antibody (Days 0, 3, 6) with or without single-fraction RT (20 Gy, Day 0). Mutational load was compared by Mann Whitney test. Times to tumor quintupling were compared using the Kruskal-Wallis test.

Results: Sarcomas from both models appeared histologically similar to undifferentiated pleomorphic sarcoma. Non-synonymous mutational load was significantly higher in the p53fl/fl + MCA model compared to the KP model (median 43 vs 0.4 mutations/MB, p < 0.01). Neither anti-PD-1 nor anti-CTLA-4 treatment resulted in significant tumor growth delay in either model. Median times to tumor volume quintupling for KP mice were 10.4 and 9.4 days with anti-PD-1 vs iso, respectively. For p53fl/fl + MCA mice treated with anti-PD-1 vs iso, median quintupling times were 9.8 and 10.3 days, respectively. For KP mice treated with anti-CTLA-4 vs iso, median quintupling times were 10.3 and 10.8 days, respectively. For p53fl/fl + MCA mice treated with anti-CTLA-4 vs iso, median quintupling times were 10.1 and 10.4, respectively. Significant growth delay occurred in all groups with RT (p < 0.01). Growth delay was similar for anti-PD-1 + RT vs iso + RT (median 24.5 vs 21.9 days for KP model; median 33.0 vs 32.0 for p53fl/fl + MCA model, respectively) and for anti-CTLA-4 + RT vs iso + RT (median 23.2 vs 19.1 days for KP model; median 31.2 and 29.8 days for p53fl/fl + MCA model, respectively). Significantly longer radiation-induced growth delay occurred in the p53fl/fl + MCA vs KP model (p < 0.001). Experiments with combined anti-CTLA-4/anti-PD-1 with and without RT are ongoing. Clonogenic assays for both tumor models are also in progress. Preliminary results indicate no difference in the in vitro radiosensitivity of the KP and p53fl/fl + MCA tumors.

Conclusions: PD-1 or CTLA-4 checkpoint inhibition does not delay tumor growth in two primary sarcoma models with significantly different mutational loads. Our results suggest that elevated mutational load is not sufficient to achieve response to immune checkpoint treatment in sarcoma, but may impact response to radiotherapy.
Clinical implications of negative direct immunofluorescence (DIF) results in Mucous Membrane Pemphigoid (MMP) with Ocular Disease

Mary Labowsky

Background: The clinical diagnosis of ocular MMP is often confirmed by biopsy demonstrating linear IgG, IgA or C3 at the dermal-epidermal junction on DIF. However, there is a considerable subset of clinically typical patients with negative DIF results; it is unknown whether this specific subgroup differs in demographics, clinical course, or prognosis, from those patients with clinically typical disease and a positive DIF. This retrospective study examined patients with clinically typical ocular MMP seen at a multidisciplinary MMP clinic and analyzed the clinical significance of positive and negative DIF results in the setting of exam findings, disease severity and progression.

Methods: We studied 106 eyes of 53 patients with clinically typical ocular MMP disease, documented DIF results, and at least 12 months of follow-up seen at the Duke University multidisciplinary MMP clinic between 1996 and 2015. We excluded subjects with a history of Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, or a presentation suspected to be secondary to antiglaucomatous medication use. We documented visual acuity, medical history (including malignancy and autoimmune disease), physical exam findings, and treatment history. Foster’s Stage and MMP Disease Activity Index (MMPDAI) were assessed at initial presentation and at 18 months.

Results: 14 of 25 (56%) subjects with ocular disease alone had positive ocular biopsy results while 26 of 28 (92.3%) with combined ocular, skin or other mucosal disease had positive biopsies (10 mucosal, 7 ocular, 6 skin, and 3 multiple biopsy sites). The proportion of subjects with a positive biopsy was significantly lower in those with ocular disease alone than in those with other tissues involved. No significant difference was seen in the severity of initial presentation or frequency of autoimmunity/malignancy between subjects with positive and negative biopsies or between subjects with ocular disease alone and those with involvement of mucosal/skin. In addition, no significant difference was seen in Foster’s Stage, MMPDAI, and vision loss from presentation and at 18 months between these subjects groups.

Conclusions: These findings demonstrate that clinically diagnosed MMP patients with isolated ocular disease frequently have negative DIF findings yet similar disease presentation and progression. The evidence from this study encourages clinicians to consider treatment of patients with clinically typical ocular MMP in a similar manner to those with a confirmatory DIF result.
Searching for Organization in Atrial Fibrillation: Recurrence Quantification Analysis of Intracardiac Electrogram Morphology and Cycle Length in Patients Undergoing Atrial Fibrillation Ablation with Focal Impulse and Rotor Modulation

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Background: Focal impulse and rotor modulation (FIRM) is a technique that may improve long-term catheter ablation outcomes in atrial fibrillation (AF) by utilizing phase-mapping of atrial waves to target drivers of AF in the atrial substrate. However, early experiences with FIRM have been mixed with widely-varying acute and long-term procedural outcomes, suggesting the need for: 1. further evidence that FIRM ablation significantly alters the global organization of AF; and 2. better intraprocedural measures to guide FIRM ablation and assess acute procedural success. Quantitative analysis of intracardiac electrograms (EGM) measured during FIRM ablation, independent of the phase-mapping techniques used in FIRM, may achieve both of these objectives. Recurrence quantification analysis (RQA) is a technique that has been used to describe temporal variations in both intracardiac EGM and surface electrocardiograms (ECG), but the optimal RQA strategy and application for EGM analysis of AF are not yet characterized. In order to test the hypothesis that FIRM ablation results in measurable AF organization on EGM, we use recurrence quantification analysis (RQA) to describe variations in EGM morphology and local AF cycle length during FIRM ablation.

Methods: In patients undergoing FIRM ablation for AF at Duke University, we retrospectively analyzed bipolar EGMs recorded with a decapolar catheter in the coronary sinus (CS) before and after ablation of each rotor. EGM analysis was performed at three CS sites using custom MATLAB code. Analysis included: (a) Ventricular activity subtraction; (b) Automated atrial wave detection; (c) Generation of local EGM morphology and cycle length recurrence plots; and finally, (d) RQA consisting of recurrence rate (RR), determinism (DET), laminarity (LAM), average diagonal line length (L), and trapping time (TT) calculations—measures which seek to quantify AF organization, with higher values suggesting increased organization. The average of these indices at the three sites were compared before and after FIRM ablation via a two-tailed Wilcoxon signed-rank test.

Results: Seventeen rotors from ten patients undergoing FIRM ablation were analyzed. Average patient age was 62.1 years, 7/10 were male, and 3/10 had paroxysmal AF. When changes in RQA parameters in three CS locations were averaged, all morphology recurrence parameters were significantly higher immediately post-rotor ablation than before. Median RR changed from 18.9% to 25.1% (p=0.006), DET from 36.3% to 47.2 (p=0.03), LAM from 44.1% to 51.3% (p=0.03), L from 1.27 to 1.45 (p=0.03), and TT from 1.45 to 1.85 (p=0.03). No significant differences in any cycle length RQA parameters were observed in any lead.

Conclusions: RQA analysis demonstrates that EGM morphology recurrence patterns and recurrence rate are significantly altered in FIRM ablation, and are altered to a greater extent than AF cycle length. These finding suggest that EGM morphology may impart crucial information regarding underlying AF organization, and that current practice of solely measuring and reporting cycle length may be inadequate to describe acute outcomes in FIRM.
A functional analysis of mixed lineage leukemia protein 2 (MLL2) in neurogenesis and the translational potential of histone deacetylase inhibition

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Background: Aberrations in histone methylation are among the most frequently implicated epigenetic changes in cancer and neurodevelopmental disorders. Mixed lineage leukemia protein-2 (MLL2) is a histone lysine methyltransferase enzyme that uniquely exemplifies this theme; a functional deficiency of MLL2 is shared in the pathophysiology of hematologic malignancies, solid tumors, and intellectual disorders. The high prevalence of aberrant MLL2 expression in human disease introduces an intriguing avenue for translational medicine in targeting the altered epigenetic profile that is associated with MLL2-deficiency. By investigating the effect of MLL2 deficiency on neurogenesis and the amenability of the MLL2-deficient neural stem cell (NSC) phenotype to pharmacologic reversal, this study aims to offer new insights into the functional role and translational value of MLL2 in diseases of the central nervous system.

Methods: Conditional MLL2 knockout mice (MLL2flfl) were crossed and NSCs were harvested at the embryonic day 14.5 time point. A Cre-LoxP system was employed to broadly delete the MLL2 allele from the MLL2flfl NSCs, and the NSCs were then cultured under differentiation conditions for seven days. Immunofluorescence with antibodies specific for mature neurons, astrocytes, and NSCs was performed and neuronal differentiation was quantified based on the presence of neuritic outgrowths positive for anti-β3 tubulin antibody staining. The therapeutic efficacy of the histone deacetylase inhibitors (HDACi) SB939 and 4-iodo-SAHA was as a means for rescuing the compromised NSC differentiation that was observed for MLL2-deficient NSCs.

Results: Adenovirus Cre-mediated deletion of MLL2 led to >90% reduction in MLL2 expression. Approximately 90% reduction in neuronal differentiation was observed in NSC lines lacking MLL2 relative to wild-type controls. This differentiation defect was confirmed across a series of six distinct NSC lines. A statistically significant rescue of neuronal differentiation was achieved via HDACi therapy. This restorative effect of HDACi pharmacotherapy was found to be time-dependent, as no increase in neuronal differentiation can be detected when NSCs are subjected to delayed HDACi therapy. Compromised differentiation capacity was found to be specific to MLL2 inactivation, as NSC lines with conditional knockdown of UTX, an enzymatic subunit of the active MLL2 methyltransferase complex, did not result in a similar phenotype.

Conclusions: MLL2 is an essential epigenetic factor in neuronal differentiation: its deficiency leads to a dramatic reduction in differentiation capacity. Partial reversal of the MLL2-deficient phenotype can be achieved via immediate HDACi therapy. However, rescue of the phenotype is lost when treatment is delayed during differentiation. These findings suggest a likely mechanism underlying pathogeneses promoted by MLL2 deficiency, and provide a rationale for exploiting HDACi as a remedy.
The influence of the menstrual phases on polysomnography.
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Background: The epidemiology of obstructive sleep apnea (OSA) exhibits a clear gender disparity; the prevalence of OSA in men is substantially higher than the prevalence in premenopausal women. This male predominance of OSA, however, disappears after menopause. The equalization of sleep apnea prevalence following menopause highlights the pivotal role of the menstrual cycle in governing patient susceptibility to OSA. Despite this established link between menstruation and OSA severity, the relative degree of sleep apnea protection that is conferred by the follicular versus luteal phase of the menstrual cycle remains undefined. Thus, the primary objective of this study is to determine how the phases of the menstrual cycle influence the results of polysomnography (PSG).

Methods: Twenty-eight adult subjects who reported regular menstrual periods, last menstrual period (LMP) within 26 days of their PSG, no exogenous hormone use, no history of polycystic ovarian syndrome, and who were scheduled for diagnostic PSG at Boston Medical Center satisfied inclusion criteria for the study. These subjects were divided into a Follicular Cohort (days 0-13 of cycle) or Luteal Cohort (days 14-26 of cycle) and a one-way analysis using a t-test was performed to test the hypothesis that the follicular phase confers protection against OSA. A likelihood-ratio chi-square test was also applied to assess for a statistically significant association between menstrual stage and the presence of moderate- to-severe sleep apnea (AHI>15/h). Thus, the statistical analysis was performed using AHI as both a continuous and a categorical outcome.

Results: The mean AHI for patients in the Follicular Cohort (6.1/h) was significantly lower than the Luteal Cohort (14.3/h, p=0.033). In the Follicular Cohort, 12% of patients had moderate to severe OSA. In the Luteal Cohort, 46% of patients had moderate to severe OSA (p=0.045).

Conclusions: The results of this study are the first to suggest that the follicular phase of the menstrual cycle has a protective effect against sleep disordered breathing in a population of premenopausal women who were being referred for diagnostic PSG with high clinical suspicion for OSA. AHI values were significantly higher for patients who underwent PSG during the luteal phase, whereas patients undergoing PSG during the follicular phase demonstrated lower overall, REM, and NREM AHI values. These findings are clinically relevant because they suggest that premenopausal patients who undergo polysomnography during the first half of their menstrual cycle may present with lower AHI values on PSG, potentially leading to inaccurate classification of OSA severity and increased morbidity. Consideration of LMP in the scheduling and interpretation of PSG is encouraged to help minimize these risks.
**Postdepletion T cell reconstitution in mice with heterologous persistent and latent viral infections**

Andie MacDonald

**Background:** Belatacept, a costimulation blockade immunosuppressant, has been successful in promoting rejection-free survival in all but a minority of patients. These patients, however, develop high rates and grades of costimulation blockade resistant rejection. The alloreactive cells responsible for this rejection are thought to be well-differentiated memory cells, likely from a variety of sources including cross-reactivity with viral-specific memory cells. T cell depletion has been shown to facilitate costimulation blockade therapy, but the dynamics of post-depletional T cells in patients with clinically significant heterologous alloreactivity have not been described. In this experiment we present a mouse model in which we examined the immune repertoire of mice infected with chronic, clinically relevant viruses that were then T cell depleted with alemtuzumab and allowed to reconstitute their T cells in the presence of absence of rapamycin.

**Methods:** CBA mice transgenic for hCD52 on T cells were mock infected with PBS or infected with polyomavirus (murine BK virus), murine CMV, and HV68 (murine EBV). Blood was collected on the day of infection and at 7, 14, 25, and 40 days after infection and analyzed by flow cytometry. At 40 days after infection, all mice were T cell-depleted with alemtuzumab, a monoclonal antibody against CD52. Two groups, one infected and one mock infected, were given rapamycin during lymphocyte repopulation, and the remaining two groups were given PBS mock injections. Blood was collected at 72 hours after depletion and every 14 days thereafter and analyzed by flow cytometry to monitor changes in the immune repertoire.

**Results:** Mice infected with viruses developed an increased CD8 memory response at 14 days after infection (p<0.01) and then returned back to baseline by 40 days after infection. Immune repertoires in both infected and non-infected groups had comparable pre-depletion immune repertoires dominated by naïve cells, but were heavily memory-skewed after antibody-mediated depletion. This appeared to be due to (1) selective memory cell sparing relative to naïve cells, and (2) rapid proliferation in the periphery reflected by increased memory cell Ki67 activity. Rapamycin-treated mice tended to have more effector memory cells than PBS-treated mice, but this trend was not statistically significant. Infected mice treated with rapamycin developed an increase in CD8+ KLRG1+ cells (p<0.01), which have been described as being viral specific in mice with chronic latent viruses.

**Conclusions:** Lymphocyte depletion resets the immune system, but depletion-resistant memory cells and rapid homeostatic repopulation create a potentially aggressive memory phenotype. However, it is also a period that yields the opportunity to favorably alter the immune repertoire. Rapamycin offers the potential to suppress alloreactivity while promoting viral memory in transplant patients, which is reflected by rapamycin-induced memory expansion and the emergence of a likely viral-specific KLRG1+ population. Further determination of the degree of alloreactivity in post-depletional cells as well as survival studies for mice in this model given heterotopic heart transplants will be helpful in gaining insight about tolerance induction.
Assessing Life’s Simple 7 in a Southeastern US Cohort: Dietary Patterns and Cardiovascular Disease

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**Background:** Life’s Simple 7 are clinical and behavioral factors that must be optimized to improve health and reach the American Heart Association 2020 goal of reducing deaths by cardiovascular disease (CVD) and stroke by 20%. One of the most challenging behaviors to optimize is healthy eating. We explored the relationship between dietary patterns, CVD prevalence, and Life’s Simple 7 adherence in a longitudinal cohort in the Southeast United States.

**Methods:** Study participants were enrolled in the Measurement to Understand Reclassification of Disease of Cabarrus/Kannapolis (MURDOCK) Study, a longitudinal population health study designed to better understand development and progression of common chronic diseases. An enrollment survey collects self-reported disease history as well as lifestyle factors, including dietary variables. Data from enrollment surveys for participants enrolled from 2/2009 to 4/2016 were used for the current analyses. Using cluster analysis, participants were grouped into distinct non-overlapping dietary groups based on dietary details provided. Logistic regression was used to model relationships between dietary patterns, baseline anthropometrics, and prevalent comorbidities controlling for age, sex, race, and, ethnicity.

**Results:** From cluster analysis, 8762 participants (mean age, 51.8 years; 67.9% female) were grouped into four distinct dietary patterns (High Produce and Dairy, Low Protein and Sweets, High Sweets and Caffeine, and High Sugar-Sweetened Beverages). The group “high sweets and caffeine” was 41% more likely to report a history of CVD than the group “high produce and dairy” (adjusted OR 1.41, 95% CI 1.10-1.79). Other dietary patterns were not significantly different for CVD prevalence compared with the “high produce and dairy.” The “high produce and dairy” group had a 19% compliance rate with the AHA diet recommendations for fruits and vegetables and sugar consumption and a 6% compliance rate overall with Life’s Simple 7 guidelines for diet, weight, blood pressure, and smoking. Overall compliance with Life’s Simple 7 was <5% for all other groups.

**Conclusions:** Few MURDOCK study participants met the AHA diet recommendations, and those who did had more favorable health status. Diet should continue to be a focus in order to reach the AHA 2020 goal.
Decreased number of neuropeptide Y positive interneurons in CA1 of hippocampus in mouse model of Alternating Hemiplegia of Childhood
Masoud, Melanie; Helseth, Ashley; Hunanyan, Arsen; Ratliff, April; Mikati, Mohamad A.

**Background:** Alternating Hemiplegia of Childhood (AHC) is a complex neurological disorder which manifests in the first 18 months of life with dystonia, hemiplegia, and seizures and progresses to developmental delay. Mutation of ATP1a3 subunit of the Na+/K+ ATPase is the primary cause of AHC. Previously, we have created a knock-in mouse model for E815K, the gene that induces the most severe phenotype of AHC. We have shown in our knock-in mouse model that there is a decrease in the number of GAD67+ (general stain for neuronal cell bodies) GABAergic interneurons as well as in the parvalbumin (fast-spiking interneuron) population in the CA1 region of the hippocampus. In this study, we quantify a sub-population of GABAergic interneurons--neuropeptide Y positive (NPY+)--in the CA1 region of the hippocampus compared to wild type. A decrease in these inhibitory interneurons in the CA1 region of the hippocampus would likely contribute to a decreased seizure threshold. We hypothesize that there is a decrease in the number of NPY+ GABAergic interneurons in the CA1 region of the hippocampus of our AHC mouse model.

**Methods:** DAB (3,3'-diaminobenzidine) immunohistochemical staining was performed to evaluate the cellularity of the hippocampus in mutant and wild type mice. Stereo Investigator software was used to quantify the number of NPY+ interneurons, and compare the cell counts between wild type mice and our AHC mouse model.

**Results:** Through stereological analysis, we found a lower number of GAD67+ GABAergic interneurons in the CA1 region of the hippocampus in our mouse model (mutant 38660 +/- 8752 vs. WT 112413 +/- 27406; p=0.0001). Additionally, there was a significantly lower number of NPY+ interneurons in this region as well (mutant 809 +/- 15 cells vs. WT 1771 +/- 26 cells; p = 0.003). There was a 55% decrease in the number of NPY+ cells in the knock-in mouse model compared to wild type.

**Conclusions:** Our finding of decreased NPY+ GABAergic interneurons shows that the abnormality in GABAergic inhibition is not restricted to our previously demonstrated reduction in fast-spiking parvalbumin positive interneurons, but also extends to the sub-population of NPY+, presumably regular-spiking, interneurons. This finding in our knock-in mouse model is a potential mechanism for the predisposition to seizures of AHC. Understanding the underlying mechanism for the phenotype may lead to novel therapies for this disorder.
Wireless, web-based interactive control of optical coherence tomography with mobile devices

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Background: The design requirements for ocular diagnostics in a general medical setting, such as the emergency room (ER), frequently differ from that of a specialty ophthalmic clinic. Optical coherence tomography (OCT) is widely used in the specialty ophthalmic setting and has the potential to be used in more general medical settings for applications such as remote diagnostics. The purpose of this work was to develop wireless interaction with an OCT system across the Internet using generally available mobile devices (e.g., cellular phones) in anticipation of remote applications.

Methods: A web-based user interface (WebUI) was developed to interact with a previously developed handheld swept source OCT system. The WebUI consisted of key OCT displays and controls ported to a webpage using only HTML and JavaScript. Client-server relationships were then created between the WebUI and the OCT probe computer across the internet using the WebSocket protocol. The WebUI was accessed on a cellular phone mounted to the handheld OCT probe for wireless control of the OCT system. 20 subjects were then imaged using the WebUI under an IRB approved protocol. Finally, the latency of the WebUI was measured using high-speed video recording of the system’s response to a light impulse.

Results: The WebUI accessed on a cellular phone was successfully used to capture posterior eye OCT images in all 20 subjects. Simultaneous interactivity with the OCT system by a remote user on a separate mobile device (laptop) was also demonstrated. Measured baseline latency of the handheld OCT system alone was 124±33ms; using the WebUI added 72±45ms and did not impact operator usage. Overall end-to-end latency of the system with WebUI was 195±67ms.

Conclusions: The novel web-based user interface allowed wireless and remote control of an OCT system across the Internet. Remote, wireless control of OCT systems is a key step towards using OCT for remote diagnostics such as for telemedicine applications. The use of the web and readily available open source software tools used in this project mean that any mobile device that can access a web page could be used for OCT control and anyone that can code a web page can rapidly customize the OCT controls for specific end-users.
Role of iNOS in lung injury development after chlorine and hydrochloric acid exposure

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Background: Inflammation is a hallmark of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), clinical syndromes characterized by diffuse alveolar injury with neutrophilic infiltrates, pulmonary vascular leak, and severe hypoxemia. ALI/ARDS can be caused by a number of inciting factors including sepsis, aspiration, and inhalation injury, which subsequently trigger an acute inflammatory response affecting the alveoli. Although the exact mechanisms underlying inflammatory injury development in ALI/ARDS are not fully understood, research highlights the potential critical role played by inducible nitric oxide synthase (iNOS), an enzyme that produces nitric oxide in the setting of inflammation.

Methods: In this study, we investigated the effects of iNOS inhibition on the development of pulmonary vascular leak in ALI/ARDS. We utilized two different animal models of ALI/ARDS: 1) a rabbit model of chlorine gas exposure with 24-hour monitoring of oxygen saturation levels, and 2) a mouse model of hydrochloric acid aspiration with bronchoalveolar lavage to measure levels of capillary-alveolar leakage. iNOS inhibition was achieved with a highly selective, irreversible inhibitor, GW274150, which was administered after chlorine or acid exposure.

Results: Our results from the rabbit model show that selective and potent iNOS inhibition with GW274150 significantly improves oxygen saturation and survival in chlorine-exposed rabbits. However, for the mouse-acid model, we observed a pattern of injury after acid instillation that was highly variable and rapidly resolving, in contrast to that previously described in the literature. Due to the highly variable injury pattern, iNOS inhibition had no significant effect on the degree of capillary-alveolar leakage in our mouse model.

Conclusions: We conclude that iNOS inhibition improves pulmonary pathology and acute survival in chlorine-induced ALI in rabbits, suggesting that excessive iNOS activity after chlorine exposure may drive inflammatory injury development. Furthermore, we conclude that GW274150 may be a candidate human therapeutic for chlorine exposure ALI/ARDS. To our knowledge, GW274150 is the first pharmacologic agent shown to be effective in reducing the morbidity and mortality of ALI/ARDS. Finally, we conclude that the mouse-acid model is not a reliable model of gastric acid aspiration ALI/ARDS, first due to its highly variable pattern of injury, and secondly due to its fast-resolving nature, which is not consistent with human ALI/ARDS.
**Why Risk Death for a Cure? A Survey of HIV Patients**
Ben Murray, Kathryn Pollak, Brian Zinkmund-Fisher, Scott Halpern, Ken Freedberg, James Hammitt, Jenny B. Barby, Regina Edifor, Nir Eyal, Peter Ubel

**Background:** The advent of highly active anti-retroviral therapy (HAART) has turned Human Immunodeficiency Virus (HIV) infection into a chronic illness for those with access to medications. Despite having a predicted length of life comparable to age-matched healthy adults, many HIV-positive people are eager to be involved in curative trials. It is important for researchers to understand the motivations of these individuals when deciding to enroll participants into potentially dangerous studies. We present the results of a survey of HIV-positive patients at two Boston hospitals to help inform future cure research.

**Methods:** Participants were age 18 or older, HIV-infected for at least 6 months, on anti-HIV therapy with stable CD4 counts, and able to read English or Spanish. The survey was distributed to a convenient sample of HIV-positive people after routine physician visits at Massachusetts General Hospital and Brigham and Women’s Hospitals from June 2015 to February 2016. Participants were approached sequentially until the desired number of completed surveys was obtained. The survey consisted of 42 questions, ranging from basic demographic information to hypothetical cure scenarios. Key topics addressed included a self-assessment of health status, stigmatization, household finances, willingness to take risk, and meaning of a cure.

**Results:** A total of 200 HIV-positive adults completed the survey. Seventy-six percent were men, and the average age was 51.9 years [SD = 10.4]. The median time since diagnosis was 19 years [interquartile range (IQR) = 13, 24 years], with the median time on HAART of 15 years [IQR = 9, 20 years]. Seventy-three percent (142 of 195) stated that they would likely take a 1 in 100 chance of death in a trial, while 26% (51 of 196) stated they would likely take a 99 in 100 chance of death. Sixty-five percent (118 of 182) expected their health to be better in five years if they were cured of HIV compared to continuing their medications. Forty-one percent (75 of 182) estimated a 50% or greater risk that the virus would stop responding to their medications. Fifty-four percent (98 of 182) of respondents estimated a 50% or greater risk of experiencing serious side effects in the next 20 years due to their medications. Seventy-nine percent (154 of 196) of respondents reported some degree of stigma. Multivariable regression using the “largest chance of death (0-100) you would accept in a cure trial” as our outcome variable failed to show any statistically significant associations.

**Conclusions:** A substantial portion of the HIV-positive people we surveyed were willing to take a significant risk of death in pursuit of a cure. A majority felt that a cure would improve upon their current health state in the short-term, and reduce their risk of negative health outcomes over the next two decades. Uncertainty existed among our study participants as to how long their current treatment regimens will remain tolerable and effective. Most participants reported experiencing stigmatization, and factors such as psychological distress, burden of medications, and altruism also motivated enrollment in trials. Such motivations have implications for the how researchers recruit and consent participants in curative studies.
Immune correlates and peripartum mother-to-child transmission (MTCT) of HIV-1 in the setting of antiretrovirals (ARVs)

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Background: More than 150,000 annual pediatric HIV-1 infections occur due to mother to child transmission (MTCT), despite the wide availability of antiretrovirals (ARVs). MTCT is unique, as HIV-exposed infants are passively immunized with maternal antibodies (Abs) before birth. Without ARVs, up to 65% of HIV-exposed infants are uninfected, suggesting that maternal antibodies may help protect infants. MTCT can occur during pregnancy/delivery (peripartum) and through breastfeeding (postpartum). Our group recently investigated immune correlates of MTCT risk in the clade B infected WITS cohort in which >50% of peripartum infections occurred during delivery. Decreased peripartum MTCT was associated with maternal anti HIV-1 envelope (Env) V3-IgG and CD4 binding site Abs, whereas high maternal tier 1 virus neutralization predicted reduced intrapartum transmission risk. As the majority of infant HIV-1 infections occur in clade C HIV-infected populations, our current study investigated if the same immune responses are associated with peripartum MTCT in a clade C, African HIV-1 infected cohort of women who received ARVs.

Methods: Plasma from the Breastfeeding, Antiretrovirals, and Nutrition (BAN) study of clade C infected Malawian mothers (n=88, 45 transmitting and 43 non-transmitting) and their infants were studied. Both women and infants received a dose of nevirapine at delivery, then one week of lamivudine and zidovudine. The majority of MTCT in this cohort was during pregnancy (91%). Binding antibody multiplex assays (BAMA) measured IgG in diluted plasma against a multiclade panel of HIV Env antigens including gp120, V3, and V1V2 constructs. Neutralization assays using a clade C tier 1 Env-pseudotyped virus and Tat-regulated luciferase reporter gene measured neutralizing capacity of maternal and infant plasma samples as reduction in viral infection of TZM-bl cells. Soluble CD4 plasma blocking ELISAs measured plasma antibodies against the CD4 binding site in clade C gp120. A multivariable logistic regression model was used to analyze the association of maternal and infant immune responses with peripartum MTCT risk.

Results: As previously reported, maternal viral load significantly predicted peripartum MTCT risk (OR 2.66, p=0.011). No significant association was detected between maternal anti-clade C V3 IgG (OR 0.57, p=0.318) or maternal tier 1 neutralization (OR 1.37, p=0.697) and MTCT risk. Unexpectedly, plasma blocking of the CD4 binding site (OR 1.06, p=0.003) and maternal anti-clade C V1V2 IgG (OR 1.62, p=0.02) predicted increased MTCT risk independent of maternal viral load. There was no association between maternal anti V1V2 IgG-specific transfer efficiency to infants and MTCT risk (OR 1.00, p=0.46).

Conclusions: This study revealed an association between high maternal CD4 binding site blocking Abs and anti-V1V2 IgG and transmission risk, while infant antibody levels and placental transfer efficiency did not predict transmission risk. Differences between the BAN and the WITS results could be due to difference in 1) transmission mode (during pregnancy versus during delivery), 2) virus clade, or 3) maternal ART. These maternal non-neutralizing antibodies associated with elevated MTCT risk could be biomarkers for increased maternal virus infectivity. Further investigations including in additional cohorts are warranted to understand the role of these antibodies during MTCT.
Primary vs. Preoperative Radiation for Locally Advanced Vulvar Cancer: A National Cancer Data Base (NCDB) analysis

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Background: For women with unresectable vulvar cancer, treatment options include primary radiation or preoperative radiation followed by surgery. The current study was conducted to evaluate patterns of care and the survival impact of primary radiation and preoperative radiation therapy with surgery in women with locally advanced vulvar cancer using a large national cohort.

Methods: Women with ≥ Stage II vulvar cancer, diagnosed from 2004-2012, who received primary or preoperative radiation therapy were identified in the National Cancer Data Base. Patient characteristics, such as age, race, cancer stage, and comorbidity score were compared between those that received primary radiation only and those that received preoperative radiation with surgery using Chi-square, Fisher’s exact, and Mann-Whitney tests as appropriate. Overall survival (OS) by treatment approaches was estimated via the Kaplan Meier method and compared using the log-rank test. Factors associated with OS were determined using univariate and multivariate Cox proportional hazards regression models.

Results: 2,046 women were identified; 1,407 (69%) of these women received primary radiation (RT) (n=421) or chemoradiation (CRT) (n=986) (RT/CRT); 639 (31%) received preoperative RT (n=92) or CRT (n=547) followed by surgery (RT/CRT+S). Staging distribution was as follows: Stage II (n=893), Stage IIIA (n=440), Stage IIIB (n=317), Stage IIIC (n=5), Stage IV A (n=254), and Stage IVB (n=137). Median follow-up was 21.9 months. Primary RT/CRT was associated with compromised OS, compared to preoperative RT/CRT+S (41.7% vs. 57.1% at 3 years respectively, p<0.001). On multivariate analysis, OS associated with primary RT/CRT with doses >55 Gy was not significantly different from RT/CRT+S (HR 1.139, 95% CI 0.969 -1.338, p=0.116). Use of concurrent chemotherapy improved OS of primary RT >55 Gy compared to CRT+S (HR 1.107, 95% CI 0.919-1.334, p=0.234).

Conclusions: In a large nationwide observational analysis, primary non-surgical management of vulvar cancer with radiation therapy was associated with compromised survival compared to preoperative radiation with surgery. However, with doses >55 Gy and concurrent chemotherapy, non-operative approaches had comparable survival compared to preoperative chemoradiation followed by surgery. These findings suggest that primary chemoradiation may be a reasonable alternative to approaches incorporating surgery. Further work is needed to identify women who would most benefit from this approach.
A Novel Monocyte Vaccine as a Simple and Highly Efficacious Immunotherapeutic for Glioblastoma
Lowell Thorndike Nicholson
Eugene A. Stead Scholarship

Background: Glioblastoma (GBM), the most common primary brain tumor, is highly aggressive and carries a particularly poor prognosis, with a median survival of <15 months. Standard therapies are ineffective and disease recurrence occurs in virtually all patients. Immunotherapies for GBM have shown some promise and evidence suggests that the activation of T cells specific for GBM antigens (Ags) can eradicate large, well-established tumors in mice and humans. Dendritic cell (DC) vaccines can be used to stimulate anti-GBM T cell responses, however, their therapeutic application has been limited by modest clinical efficacy, the complexity of their preparation, and high costs. We have identified a novel vaccine strategy in which freshly isolated monocytes are loaded with tumor-specific antigen (Ag) and immediately administered intravenously (IV) to stimulate robust T cell proliferation, cytotoxic T lymphocyte (CTL) activity, and antitumor responses that are far superior to those seen with currently available cancer vaccination strategies. Although preliminary data have shown potent antitumor immune responses with model Ag-loaded monocytes, vaccination with endogenous tumor Ags has not yet been evaluated. The overall objective of the present study is to determine the efficacy of monocyte vaccination using the GBM-specific tumor antigen, mutant isocitrate dehydrogenase 1 (mIDH1).

Methods: Mouse monocytes were purified from total bone marrow using negative selection. To determine optimal Ag loading conditions, purified monocytes were incubated with increasing concentrations of FITC-labeled OVA peptide or lipofectamine-treated EGFP at 37°C 5% CO₂ and analyzed using flow cytometry. Ag-specific immune responses were detected in vivo by measuring the proliferation of Ag-specific T cells in monocyte vaccinated recipient mice. The efficacy of checkpoint blockade was assessed by combining monocyte vaccination with either anti-PD-1, anti-PD-L1, or anti-CTLA4 antibody treatment in a murine melanoma model. For in vivo GBM tumor experiments, CT2A tumor cells expressing mIDH1 were implanted into the right caudate nucleus of female C57BL/6-WT mice via stereotaxic surgery. Tumor bearing mice were treated with mIDH1-loaded monocytes plus anti-PD1 antibody (n=8) or anti-PD1 antibody alone (n=10). As a negative control, each treatment group was compared to a cohort of untreated (tumor alone) mice (n=10).

Results: We find that monocytes actively take up peptide antigens and can be efficiently transfected with mRNA using lipofection. Additionally, we observe that immunization with peptide- and mRNA-loaded monocytes induces proliferation of Ag-specific T cells and that checkpoint blockade enhances the efficacy of monocyte vaccination. Finally, we find that vaccination with mIDH1-loaded monocytes in combination with checkpoint inhibition significantly prolongs overall survival in mice with highly aggressive gliomas.

Conclusions: Taken together, these findings suggest that a monocyte-based cellular vaccine could serve as a simple and efficacious antitumor therapeutic, especially in cancers for which standard therapies are not particularly effective. If translatable to humans with GBM, our vaccine strategy could be quickly and easily brought into the clinical setting, providing a much needed alternative to traditional therapies.
Ganglion Cells Control Spatial Patterning of Astrocytes to Guide Angiogenesis During Retinal Development

Matthew L O’Sullivan and Jeremy N Kay

**Background:** Retinal astrocytes migrate into the retina from the optic nerve (ON) during embryonic development and spread centrifugally in the nerve fiber layer (NFL) to cover the inner retina. Astrocytes guide development of the intrinsic retinal vasculature, but factors that pattern the astrocyte template itself remain elusive. This problem is significant because defects in astrocyte-vascular development underlie retinopathy of prematurity (ROP) and the pathogenesis of ROP remains poorly understood. We propose that astrocytes use RGC axons as directional cues and will not achieve proper spatial distribution in retinas lacking retinal ganglion cells (RGCs). We tested this hypothesis by investigating astrocyte development in mice lacking RGCs through genetic ablation of *Math5*, a transcription factor required for RGC fate specification.

**Methods:** Eyes from *Math5* null and littermate control mice were fixed at different postnatal ages, and retinas removed, immunostained, and imaged by confocal fluorescence microscopy. Antibodies against Pax2, PDGFRα, CD31, RBPMS, and neurofilament were used to label astrocytes, blood vessels, and RGCs in flat-mounted retinas.

**Results:** Astrocytes are intimately associated with RGC axons during their migratory phase of development. Without RGCs, astrocytes are delayed in their centrifugal migration and intrinsic retinal vasculature does not emerge. Astrocytes fail to distribute themselves with homogenous density across the retina, instead accumulating in abnormally high density in the center of *Math5* null retinas. The astrocyte network that does form is immature and dysmorphic, lacking the regularity and polarization characteristic of wildtype retinas. Immature astrocytes are associated with RGC axon fascicles, and loss of RGCs randomizes their orientation during migration.

**Conclusions:** RGCs are required to cover the retina with astrocytes and to form a normal astrocyte network. Our data show that RGCs provide a directional cue to orient and polarize developing astrocytes, and the close relationship between migrating astrocytes and RGC axon fascicles suggests a contact-mediated interaction. Subsequently, intrinsic retinal vasculature fails to develop in the absence of a well-patterned astrocyte template. These data support a model in which astrocytes are critical for coordinating neuroretinal development with angiogenesis, with RGCs guiding astrocytes which in turn instruct blood vessels. Understanding molecular mechanisms of retinal neuro-glial-vascular interactions may identify novel therapeutic targets for treatment and prevention of ROP and other vascular disorders.
Cartilage Strain Increases with Increasing Duration and Speed of Exercise
Chinmay Paranjape¹, Gangadhar Utturkar¹, Amber Collins¹, Daniel Schmitt², William Garrett¹, Charles Spritzer¹,³, Louis DeFrate¹,³
Duke Translational Medicine Institute (DTMI) Scholarship

Background: Joint degeneration resulting from cartilage injury and leading to osteoarthritis is a serious, multifactorial problem in the United States and worldwide. Regular exercise and associated fitness has clear health benefits. However, due to increasing incidence of over-use injuries in the recreational population, there may be concern about increasing the intensity or frequency of joint loading, leading to hesitancy to exercise. Little is known about the extent of cartilage strain during normal exercise as a function of both duration and speed.

Methods: Ten healthy adults with no history of injury or surgery to either lower extremity participated in this IRB approved study. Subjects walked at a comfortable walk speed (normalized to their height) at various durations and were then given the opportunity to participate in a separate protocol that varied speed. Resting baseline cartilage thickness values were obtained prior to each walk. Subjects were transported via wheelchair to an adjacent room where they walked on a treadmill at the appropriate duration, speed combination. Then, post-activity imaging was obtained to assess cartilage deformation quantitatively in three dimensions. Statistical differences were determined using spearman rank order coefficients (P < 0.05) and chi-squared goodness of fit tests to a simple exponential approach function.

Results: With increasing walk duration at a comfortable walk speed, cartilage strain increased in a manner that was approximated by a simple exponential approach function. Strain increases with increasing walk speed from a slow walk to speeds approaching the run-walk transition.

Conclusions: This study demonstrates, for the first time, that the physiologic evolution of in-vivo strain in the knee during walking does not approach levels that endanger cartilage, with a maximum strain of approximately 8% and a known dangerous level of between 25 and 80% strain upon single impact. This in turn suggests that prolonged exercise and exercise at high speeds does not increase risk of cartilage damage. Furthermore, this data gives us knowledge of how cartilage is deforming in vivo which may inform boundary conditions for studying cartilage explants in situ. Results of this study support this research methodology as a useful mechanism for evaluating the efficacy of different surgical interventions for restoring normal joint mechanics.
Loss of MAFB function in humans and mice causes Duane syndrome, aberrant extraocular muscle innervation, and inner-ear defects

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Background: Duane syndrome is a congenital eye movement disorder defined by limited outward gaze of the eye, and retraction of the globe on attempted inward gaze. Autopsy and brain imaging studies of patients have found that the abducens nerve is absent or hypoplastic, and that the lateral rectus extraocular muscle is aberrantly innervated by a branch of the oculomotor nerve instead of the abducens nerve. Although this pathology has been well characterized, the developmental etiology of Duane syndrome remained unknown. In this study, we identify novel mutations in the gene MAFB that cause Duane syndrome and inner-ear defects, and establish the first animal model of the disorder.

Methods: We performed targeted screening of 410 patients with Duane syndrome for mutations and copy number variations in MAFB. We generated Mafb knockout mice and crossed them to Islet:GFP reporter mice to label the motor axons. Mafb is expressed in the hindbrain but not the midbrain in early development, and removing Mafb disrupts the development of the abducens nerve but not the oculomotor nerve. We used a novel orbital dissection technique and stained with a conjugated smooth muscle actin antibody to visualize the developing cranial nerves and extraocular muscles in mouse embryos. We imaged with a Zeiss confocal microscope, measured nerve diameters in Zen, and analyzed the quantitative data in Graphpad Prism. We characterized the expression of mutant MAFB transcripts in vitro from patient-derived lymphoblast cell lines transformed from whole blood. We then modeled the transcriptional activities of the mutant transcripts with a luciferase assay, using constructs containing a MAFB recognition element.

Results: We identified three heterozygous loss-of-function mutations in MAFB causing Duane syndrome and a putative dominant-negative mutation in MAFB causing both Duane syndrome and inner-ear defects. We observed that Mafb knockout mice recapitulate the human phenotype, and that selectively disrupting abducens nerve development is sufficient to cause secondary innervation of the lateral rectus muscle by aberrant branches of the oculomotor nerve. We further characterized the aberrant branching, and found that the oculomotor nerve forms both a proximal and a distal aberrant branch, which arise at native decision regions close to target extraocular muscles. We demonstrated in vitro that the putative dominant-negative MAFB transcript was expressed in lymphoblasts derived from the patients with both Duane syndrome and inner-ear defects. We measured the transcriptional activity of the mutant MAFB protein by luciferase assay, and found that it acted in a dominant-negative fashion. Through genotype-phenotype correlations in humans and mice, we proposed a threshold model for variable loss of MAFB function causing Duane syndrome and inner-ear defects.

Conclusions: Loss of 50% MAFB function is sufficient to cause Duane syndrome, while greater than 50% loss can cause both Duane syndrome and inner-ear defects. Furthermore, the primary etiology of Duane syndrome is failure of the abducens nerve to fully innervate the lateral rectus muscle during development.
Free Mitochondria are Taken Up by Antigen Presenting Cells and Increase Activation
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Stead Scholarship, Bollinger Scholarship, Poindexter Fellowship, ASTS Student Mentor Grant

Background: Antigen presenting cells (APCs), including dendritic cells (DCs) and macrophages (MPs), are key inducers of alloimmunity through antigen presentation, costimulation, and cytokine production. However, the mechanisms of APC activation in the setting of tissue injury remain incompletely understood. Cellular injury, such as that seen in ischemia-reperfusion and surgery, has been shown to activate APCs, and evidence suggests a role for mitochondria at this interface between injury and immunity. To investigate this, we have explored cellular uptake of mitochondria, APC activation, and immune responses to mitochondria and their components.

Methods: Immature bone marrow-derived DCs and MPs were produced by culture with GM-CSF or M-CSF, respectively. MPs and DCs were co-cultured with purified cytosolic, microsomal, and mitochondrial cell fractions. Subcellular fractions from cultured LMTK fibroblasts or homogenized murine livers were separated by differential centrifugation alone or followed by affinity beads. Supernatant cytokines and cell surface activation markers were measured to assess immunophenotypes. Mixed lymphocyte reactions (MLR) with cell fraction-treated DCs and transgenic OT2 murine T cells were employed to evaluate the adaptive immune response. Mitochondrial uptake was evaluated by flow cytometry and confocal microscopy of immortalized DC and MP cell lines co-cultured with purified mitochondria stably labeled with dsRed or GFP.

Results: Differing mitochondrial separation methods produced varying phenotypes. Incubation with affinity-separated mitochondria activated DCs, indicated by markedly increased costimulatory expression (CD40, CD86, and MHC II) and increased production of cytokines (IL-6 and TNF-α) as compared to other cell fractions. This upregulation of CD40 and cytokines showed dose-dependence. This innate immune activation was not observed with mitochondrial fractions separated by differential centrifugation alone, and preliminary data suggests affinity separation procedure may have damaged mitochondrial polarization and/or structure. DCs and MPs readily took up free mitochondria. This uptake was lasting and not fully blocked by inhibition of phagocytosis. Notably, though activation of overall cell populations was not significantly changed, uptake-positive DC and MP subpopulations in treated cultures showed higher expression of activation markers (CD40, CD80, and MHC II) than uptake-negative subpopulations in the same cultures.

Conclusions: We have shown that purified mitochondria can be potent activators of DCs and are sufficient to produce the downstream signals necessary for mounting an adaptive immune response. Based on results differing by purification method, we suspect this to be specific to the setting of compromised mitochondrial health, though this is still under investigation. This innate immune activation was specific to mitochondria and not observed with other subcellular fractions. We have also demonstrated durable uptake of free mitochondria in activated DC and MP subpopulations. These data suggest that the release of mitochondria may be a critical mediator of immune activation in the setting of tissue injury. Uptake of mitochondria presents further novel therapeutic potential both within and beyond the realm of immunity.
What Factors Drive Inpatient Satisfaction After Knee Arthroplasty?
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Background: The HCAHPS (Hospital Consumer Assessment of Healthcare Providers and Systems) Survey, developed by the Centers for Medicare & Medicaid Services (CMS), is the first national, standardized, publicly reported survey of patients' perspectives of hospital care. It is well established that surgical patients’ perception of inpatient care has a significant effect on choice of healthcare provider. The purpose of this study was to analyze survey responses from patients who underwent primary knee arthroplasty in order to identify factors that drive patient satisfaction in the inpatient setting.

Methods: HCAHPS responses received at our institution between January 1, 2013 and January 1, 2016 were obtained and expressed as a percentage of overall satisfaction. We analyzed the survey domains involved in the CMS Value Based Purchasing, including communication with doctors, communication with nurses, communication about medicines, pain management, hospital environment, discharge information, and overall hospital rating. Patient demographics, insurance type, prior narcotic use, preoperative pain score, length of stay, and distance to surgical center were recorded. Categorical variables were correlated to overall satisfaction with the Kruskal-Wallis test. We utilized a linear regression model to correlate nominal variables with overall satisfaction.

Results: Overall, responses from 582 patients who underwent knee arthroplasty were obtained (556 Total Knee Arthroplasty, 26 Unicompartmental Knee Arthroplasty). There was a statistically significant difference in overall satisfaction when comparing sex (p=0.036), race (p=0.03), and socioeconomic status (p<0.001). Males reported a higher satisfaction than females (77.8% vs 74.2%). Patients in the 1st quartile of socioeconomic status reported a higher satisfaction than those in the 4th quartile (81.3% vs 71.3%). African American patients reported a higher satisfaction than Caucasian and Other races (81.8% vs 76.5% vs 66.3%). There was an inverse relationship between increased length of stay and reported satisfaction (R=-0.113, p<0.001). There was no significant correlation between satisfaction and insurance type, smoking status, marital status, pain score, narcotic use, age, or distance to surgical center.

Conclusions: Patient-reported satisfaction has become an increasingly important assessment of physician and hospital staff care. The CMS now utilizes the HCAHPS survey as a measure for hospital reimbursement. Our data indicate that patients who are likely to report higher levels of inpatient satisfaction after knee arthroplasty are male, African American, of lower socioeconomic status, and with shorter length of stay. This indicates that orthopedic surgeons should aim to minimize length of stay when possible, and suggests a potential role for targeted interventions in patient groups with low satisfaction. To our knowledge this is the first reported analysis of the HCAHPS survey in relation to total joint arthroplasty.
Bland embolization versus radioembolization for the treatment of HCC in cirrhotic patients: Impact on hepatic function

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Background: Multiple hepatic arterial embolotherapies have shown similar objective tumor responses for the treatment of hepatocellular carcinoma (HCC) but the degree of resulting hepatic impairment is also an important factor. The purpose of this study was to analyze the impact of bland embolization and radioembolization on the Model for End-Stage Liver Disease (MELD) score over time.

Methods: Analysis was performed on 132 patients undergoing first-time treatment of HCC in a lobar or bilobar fashion with radioembolization (n= 53) or bland embolization (n=79). The total bilirubin, creatinine, and INR levels were ascertained immediately pre-procedure and at 1, 6, and 12 months after treatment to calculate MELD scores. Chi square tests were employed to compare MELD scores to baseline for each modality.

Results: Baseline pretreatment MELD for TARE vs. TAE was 8.9 and 11.0, respectively. With radioembolization, there was a significant increase in the mean MELD score at each time point compared to baseline: 10.9 at 1 month (p=0.001), 13.6 at 6 months (p<0.001), and 15.4 (p<0.001) at 12 months. With bland embolization, the differences were less significant: 12.0 at 1 month (p=0.081), 12.8 at 6 months (p=0.002), and 13.1 at 12 months (p=0.003). The percentage of patients with increases of 4-points or more at 1 and 6 months were similar, but at 12 months post-treatment, patients undergoing radioembolization were significantly more likely to have a 4-point or greater increase: 62.1% versus 25.9%, p=0.001.

Conclusion: Patients undergoing treatment for HCC with radioembolization had a more pronounced increase in MELD score over time compared to bland embolization, which suggests that bland embolization may result in less collateral damage than radioembolization when used in a lobar manner.
Lymphovascular Invasion is Associated with Compromised Survival for Papillary Thyroid Cancer


**Background:** Data regarding the association between tumor lymphovascular invasion and survival for patients with papillary thyroid cancer (PTC) are limited. This study sought to examine lymphovascular invasion as an independent prognostic factor for patients with PTC undergoing total thyroidectomy.

**Methods:** The National Cancer Data Base (2010-2011) was queried for all patients with a diagnosis of PTC who underwent total thyroidectomy. Patients were classified into two groups based on the presence/absence of lymphovascular invasion. Demographic, clinical, and pathologic features at the time of diagnosis were evaluated for all patients. A Cox proportional hazards model was developed to identify factors associated with survival.

**Results:** In total, 40,324 patients met inclusion criteria; 12.5% had lymphovascular invasion. Patients with lymphovascular invasion were more likely to have larger tumors (2.8 cm vs 1.6 cm, absent lymphovascular invasion, p<0.01), metastatic lymph nodes (75.1% vs 34.1%, p<0.01), and distant metastases (3.1% vs 0.5%, p<0.01). They also were more likely to receive radioactive iodine when compared to patients with tumors without lymphovascular invasion (70.2% vs 48.7%, p<0.01). Unadjusted 5-year overall survival was lower for patients with tumors with lymphovascular invasion (86.1%) compared to patients without it (94.2%) (log-rank p<0.01). After adjustment, increasing patient age (HR=1.06, p<0.01), male gender (HR=1.63, p<0.01), presence of metastatic lymph nodes (HR=1.73, p<0.01), presence of distant metastases (HR=4.90, p<0.01), and presence of lymphovascular invasion (HR=1.99, p<0.01) were associated with compromised patient survival. Treatment with radioactive iodine improved survival for patients with tumors with lymphovascular invasion (HR=0.42, p<0.01) and those without (HR=0.48, p<0.01).

**Conclusion:** The presence of tumor lymphovascular invasion among patients undergoing total thyroidectomy for PTC is independently associated with compromised survival. Patients with PTC with lymphovascular invasion should be considered higher risk, and should undergo adjuvant RAI treatment.
Modifying Hernia Mesh Design to Improve Device Mechanical Performance and Promote Tension-Free Repair
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Background: Two million laparotomies are performed annually in the United States. Ventral hernias are a frequent complication in 10-30% of patients. Nearly all ventral hernias are caused by tension on the midline. Dissipation of tension to the lateral abdominal wall is critical for successful hernia surgery. Hernia repairs have five main failure modes: suture breaking, knot unraveling, suture-mesh disruption, mesh rupture, and tissue failure. To design a device to overcome these failure modes, we sought to characterize suture and mesh mechanical properties and design a novel hernia device for hernia repair.

Methods: Uniaxial static tensile testing was conducted on polypropylene suture and a composite mesh to evaluate the mechanical properties of each implantable device. Using a tensometer, the breaking strength, knot breaking strength, mesh pull-out force, and tissue pull-out force of both suture and mesh were compared. Subsequently, the ultimate tensile strength (UTS) of a standard of care (SOC) mesh anchored with three sutures and a novel hernia mesh anchored with mesh extensions was evaluated in a swine abdominal wall model. The novel hernia mesh application parameters (stitch pattern and throw count) and design parameters (interspace distance and extension width) were varied and compared to the SOC mechanical performance. The novel hernia device was then implanted into a live Yucatan pig for 30 days to evaluate inflammation and bio-incorporation according to FDA ISO 10993 Annex E.

Results: The mean suture breaking strength, knot breaking strength, mesh pull-out force, and tissue pull-out force was 52.6±0.6 N, 51.2±3.9 N, 33.4±8.1 N, and 87.13±5.8 N, respectively. The mean mesh breaking strength, knot breaking strength, and mesh detachment force, and tissue pull-out force was 92.8±6.2 N, 83.3±14.3 N, 101.9±9.5 N, and 121.1±22.5 N, respectively. When applied to a bench-top abdominal wall model, the SOC mesh had a mean UTS of 12.7±4.1 N/cm, while the prototype mesh had a mean UTS of 38.8±14.6 N/cm across all testing parameters (Figure 1A-D), p=0.0003.

After 30 days of implantation in a Yucatan swine, there was no significant difference between inflammation and bio-incorporation scores.

Conclusions: Testing demonstrates that the novel mesh design has a stronger breaking strength, knot strength, and anchor retention as compared to polypropylene suture. When applied in an acute rupture bench-top model, the novel mesh is able to withstand significantly higher stress as compared to the current S.O.C. mesh. Based upon these results, it would be expected that when applied in a human, the novel mesh would be less susceptible to failure and therefore, hernia recurrence would be significantly reduced. The foreign body reaction of the novel mesh is equivalent to the current standard of care mesh.
Role of post-translational modifier Hipk2 in Acute Myeloid Leukemia

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Background: Homeodomain-interacting protein kinase 2 (Hipk2) is one of a family of highly conserved serine-threonine kinases known to phosphorylate key tumor suppressors like p53 as well as play a key role in hematopoiesis. This kinase activity can modulate processes like activating apoptosis, inhibiting angiogenesis and tumor growth. Mutations in Hipk2 have been implicated in the progression of tumor development. It is our hypothesis that the progression to Acute Myeloid Leukemia (AML) could be caused by mutations in Hipk2 that disrupt its normal function.

Methods: Hipk2 was found to be aberrantly repressed by the expression of the AML fusion gene, MLL-AF9, in the THP-1 pediatric AML cell line. We sought to determine the role of Hipk2 in leukemogenesis in infant AML by overexpressing normal Hipk2 in the THP-1 cell line. We have previously identified that Hipk2 plays a significant role in erythroid development. An in vitro system of primary mouse myelopoiesis was used to observe granulocyte differentiation. Using murine lineage-depleted hematopoietic stem cells, we observed the effects of Hipk2 knockdown using retroviral shRNA. We then collected aliquots at regular intervals for analysis by cytometry and cytospin for daily cell counts as well as progress towards granulocyte maturation.

Results: Preliminary results suggest decreased expression of granulocyte differentiation (indicated by reduced GR1 surface marker expression) in Hipk2 knockdown cells compared to control cells. Interestingly, these same cells show an increase towards the macrophage lineage (indicated by increased Mac1 expression). Of note, we have also observed decreased GR1 expression in THP-1 cells when compared to control cells.

Conclusion: Decreased expression of GR1 in Hipk2 knockdown cells may reveal a role for Hipk2 in granulocyte differentiation.
**Novel mouse model of dystonia**
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Ruth K. Broad Medical Fellow in the Neurosciences Award

**Background:** Dystonia is a neurological movement disorder characterized by involuntary twisting movements and abnormal postures. DYT1 dystonia is an autosomal dominant, early-onset, generalized dystonia associated with a deletion in the Tor1a gene, which encodes the TorsinA protein. Despite motor abnormalities in human patients, heterozygous DYT1 mouse models do not exhibit robust phenotypes. The F205I mutation is a rare mutation in the Tor1a gene, identified in a case of sporadic, late-onset focal dystonia. To determine the behavioral significance of the F205I mutation, a knock-in mouse model was created.

**Methods:** Mice wildtype, heterozygous, and homozygous for the F205I mutation were tested on the novel open field, home cage open field, accelerating rotarod, treadmill, wire hang, and grip strength tests.

**Results:** Mice homozygous for the F205I mutation moved less in the novel open field, though not the home open field. Homozygous mice fell faster on the first day of the accelerating rotarod and not on subsequent days of testing. Homozygous mice were unable to run at the same speed as wildtype mice on the treadmill and performed worse on the wire hang than wildtype mice. Wildtype and F205I homozygous mice had similar grip strength.

**Conclusions:** Mice homozygous for the F205I mutation have robust motor deficits not previously observed in the DYT1 mouse model. Motor deficits occur when homozygous mice are exposed to a new environment, suggesting that novelty/stress may induce motor impairments. The motor deficits of F205I homozygotes therefore provides the opportunity to study a behaviorally symptomatic mouse model of dystonia.
The Effect of Sponge Versus No-Sponge Placement of Mitomycin-C on the Outcomes of Trabeculectomy with Ex-PRESS Glaucoma Filtration Device

Michael S. Quist, B.S., Ninita Brown, M.D., Ph.D., Amanda E. Kiely, M.D., Sandra Stinnett, DrPH, Leon W. Herndon, M.D.

Background: Trabeculectomy with Ex-PRESS glaucoma filtration device is one of the many surgical treatments for glaucoma. The implantable shunt is a non-valved implant that allows for the flow of fluid from the eye to the subconjunctival space. Unfortunately, in certain cases scarring in the subconjunctival space can lead to elevated intraocular pressure (IOP). In efforts to decrease scarring during trabeculectomy, many surgeons place mitomycin-C (MMC) under the conjunctiva prior to placing the implantable Ex-PRESS shunt device. Traditionally, MMC is applied to the tissues by using surgical sponges. However, alternate modes of application exist. This study assesses the overall success rates and complication rates between patients who receive MMC using a sponge vs no-sponge (injection of MMC) as well as the final IOP lowering effects and bleb characteristics between the groups.

Methods: 100 patients were enrolled and each patient was randomized to one of the two treatment groups. The attending physician was masked as to the status of this randomization. Patients were followed for 6 months. The primary outcomes assessed were IOP and bleb morphology. Secondary endpoints included complications such as bleb failure, bleb leaks, bleb encapsulation, hypotony, hypotony maculopathy, choroidal effusions, choroidal hemorrhage, the need for laser suture lysis, bleb needling, restarting pressure lowering agents, application of 5-FU, bleb revision, or subsequent glaucoma surgery.

Results: 95 eyes were analyzed. There was no significant difference in IOP reduction between groups; however the injection group had higher rates of hypotony (p=0.007) but with no increase in adverse outcomes. Patients who had trabeculectomy/Ex-PRESS alone had greater IOP reduction than those who had concurrent cataract surgery (p=0.002). The sponge group had higher rates of 5-FU use (p=0.002) and higher reoperation rates (p=0.043) when compared to the injection group. The sponge group required a 12% reoperation rate compared to a 0% reoperation rate in the injection group. Additionally, it was found that using circumferential sutures to close the conjunctiva resulted in less astigmatism than when using radial wing sutures (p=0.037).

Conclusions: This is the first prospective study to look at the difference in the two methods in terms of IOP lowering effect as well as complications. Injection of MMC seems to be a superior option to application with a sponge; though injection provides similar IOP reductions, it decreases the need for further clinical and surgical intervention after trabeculectomy when compared to the sponge application method. Overall, we propose several measures to increase the efficacy and success of trabeculectomy with Ex-PRESS shunt while decreasing complication rates. These measures include subconjunctival injection of MMC as opposed to sponge application, avoiding concurrent cataract surgery, and utilizing circumferential sutures to close the conjunctiva. Together, these strategies will help to reduce failure rates, slow glaucoma progression and significantly increase patients’ quality of life by decreasing the amount of post-op procedures necessary.
The Effect of Scheduled Ripcord Removal on the Outcomes of Baerveldt 350 Implants

Michael S. Quist, B.S., Sandra Stinnett, DrPH, Leon W. Herndon, M.D.

Background: The Baerveldt implant is a non-valved drainage device that is used in the surgical management of refractory glaucoma. To prevent hypotony, a ligature is used to hold back the flow of aqueous humor in the immediate post-operative period and this ligature typically dissolves within 4-6 weeks. For more controlled management of intraocular pressure (IOP), a ripcord (suture) can be inserted into the lumen of the Baerveldt tube. This ripcord can be removed prior to the ligature dissolving. This allows for the opening of the tube in a controlled setting such that complications of hypotony (excessively low IOP) can be managed. In comparison, when the ripcord is not removed, the IOP may drop spontaneously and suddenly when the absorbable ligating suture dissolves, potentially placing the patient at increased risk for complications associated with hypotony. This study is comparing the complication rates after scheduled ripcord removal at three weeks versus spontaneous tube opening.

Methods: This is a randomized prospective study looking at outcomes and complication rates after scheduled ripcord removal versus no ripcord removal amongst glaucoma patients at Duke Eye Center. The ripcord was scheduled for removal on post-operative week 3 in the intervention group. Complications assessed include hypotony, central anterior chamber depth, choroidal effusions, choroidal hemorrhage, hyphema, hypopyon, fibrinous reaction, tube migration and infection. Variables were analyzed using the Student t test and Fisher exact test to determine the association between postoperative complications after removal at three weeks and complications at 4-6 weeks. A p-value of 0.05 or less was considered statistically significant.

Results: A total of 41 eyes were analyzed, with 22 eyes in the ripcord removal group and 19 eyes in the observation group. There was a significant difference in the postoperative IOP at the 3-month visit between the ripcord removal group and the observation group. These pressures were 15mmHg and 12mmHg respectively (p=0.03). A fibrinous reaction was noted in four patients in the observation group compared to the ripcord removal group in which no patients had such a reaction. (p=0.02). With respect to other postoperative complications, there were no statistically significant differences in the proportions of patients who developed hypotony, choroidal effusions, choroidal hemorrhages, hyphema and infection in the ripcord removal group and the observation group. Hypotony occurred in 4 eyes in the ripcord removal group at the 5th week follow up visit, with this number decreasing to 1 eye by the 6 month follow up visit.

Conclusions: This is the first prospective study to look at the difference in these two methods in terms of IOP lowering effect as well as complications. This study suggests that there is no difference in the incidence of hypotony, choroidal effusions, choroidal hemorrhages and hyphema after scheduled ripcord removal compared to spontaneous tube opening. Current data also suggests that compared to ripcord removal, spontaneous opening of the Baerveldt is associated with a higher incidence of developing a fibrinous reaction around the implant.
Computational Integration of Clinical and Geographic Data in a Diabetic Population

Adrian Randall, Erich Huang MD/PhD

**Background:** Social and geographic factors have been shown to broadly have an impact on overall population health, and there is a need to identify local factors that may play a role in the health of patients in the greater Durham community. As identified by the national Healthy People 2020 project\(^1\), geographic factors associated with population health include items such as access to grocery stores, parks, healthcare, and others.

**Methods:** To identify social and geographic factors contributing to health outcomes, clinical data sets from the Lincoln Community Health Center as well as the Southeastern Diabetes Initiative (SEDI) were analyzed in conjunction with publically-available GIS data from providers like Factual, Durham County, and others to develop predictive models for clinical variables such as average-A1c values for diabetic patients. GIS data used included average nearby property value as well as proximity to supermarkets, pharmacies, tobacco shops, fast food, and convenience stores. Clinical data included patient location and age. Modeling was performed using Random Forest Regression.

**Results:** Results from Random Forest Regression models where clinical data were combined with geographic data were weakly predictive for average A1c values. For predicting average A1c values in a diabetic patient population, in order from most to least important, input variables most strongly predictive were age and mean surrounding property value.

**Conclusions:** While results from this study were limited, as clinical data sets become more comprehensive, the inclusion of social and geographic factors to analyses may yield better predictions of clinical outcomes in patients.

\(^1\) https://www.healthypeople.gov/2020/leading-health-indicators/2020-lhi-topics/Social-Determinants
Lowering the Barrier of Surgical Endoscopy with a Novel Articulating Retractor

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Background: Surgical endoscopy has gained expertise and popularity over the past several decades and is a viable option for minimally invasive removal of benign and early malignant lesions in the gastrointestinal tract. Surgical endoscopy utilizes natural orifice access which shortens hospital stay, minimizes patient discomfort, and decreases overall healthcare costs. However, the inability to effectively retract and position target tissue is a significant limitation of these procedures. Endoscopic “biopsy” working channels, ranging from 2.8mm to 6.0mm in diameter, are the surgeon’s only access for intervention, and current instruments can only be manually withdrawn or advanced through the channels. As a result, the surgeon must manipulate the endoscope itself to create an appropriate dissection plane, often obscuring visualization of the plane in the process. There is a tangible need to provide better access and control of soft tissue to be able to perform more complex and complete endoscopic resections.

Methods: We have developed a novel device to provide optimal tissue retraction for endoscopic procedures. Our device consists of an articulating tissue retractor and a specialized handle that allows for single-hand operation. We created two “curves” that can manipulate the position and direction of the retractor tip by attaching wires to two different articulation points on the retractor. Each curve is independently adjusted by locking thumb sliders on an intuitively designed handle, allowing for increased range of motion and retraction independent of endoscope position. Slip strength and distal tip deflection was tested in porcine GI tract using the novel articulating retractor as well as a Boston Scientific Radial Jaw 4, a commonly used grasper for surgical endoscopy. Slip strength testing was used to determine the peak force needed to cause the retractor to slip off various types of tissue. Distal tip deflection testing was used to measure the range of motion of the conventional grasper as compared to the articulating one.

Results: The mean slip strength of the articulating retractor was slightly greater than the conventional retractor in the cardia (1.02N +/- 0.45 vs. 0.96N +/- 0.39N, p-value: 0.373), greater curvature (1.48N +/- 0.41 vs. 1.41N +/- 0.74N, p-value: 0.408), and antrum (1.14N +/- 0.49 vs. 1.08N +/- 0.33N, p-value: 0.381). It was slightly lower in the lower esophagus (0.90N +/- 0.40 vs. 0.99N +/- 0.40N, p-value: 0.695). While this may be the case, both retractors produced on the order of 1N and is statistically insignificant. In distal tip deflection, curve 1 produces the maximum deflection at 72° and also changed the orientation of the jaws from horizontal to slightly beyond vertical. When curve 2 was tested, the entire grasper only lifted by 24°, but the tension on the knuckles made them buckle. When both curve 1 and 2 were activated, an S-shaped curve was formed, with preserved retractor orientation and a 30° retractor deflection. Finally, in the case of conventional retractor, it was only able to engage in axial rotation, and it remained stationary when fixed at the base.

Conclusions: The nascent field of surgical endoscopy is gaining popularity but still remains hindered because of the inability to triangulate tissue. We have developed a novel retractor that has similar slip strength compared to the current gold standard, but has much wider range of motion. This is critical because it allows for tissue resection without using the endoscope itself as counter-traction. It will lower the barrier for entry into surgical endoscopy and allow it to gain adoption.
Integrating Heart Rate Variability, Vital Signs, Electrocardiogram, and Troponin to Triage Chest Pain Patients in the Emergency Department
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Background: Current triage methods for chest pain patients typically utilize symptoms, electrocardiogram (ECG), and vital sign data, requiring interpretation by dedicated triage clinicians. In contrast, we aimed to create a quickly obtainable model integrating the objective parameters of heart rate variability (HRV), vital signs, troponin, and ECG to improve accuracy and efficiency of triage for chest pain patients in the Emergency Department (ED).

Methods: Adult patients presenting to the ED with chest pain from September 2010 to July 2015 were prospectively recruited. Patients with obvious non-cardiac etiologies or irregular/non-sinus rhythm on ECG were excluded. Primary outcome was a composite of revascularization, death, cardiac arrest, cardiogenic shock, or lethal arrhythmia within 72-hours of presentation to the ED. To create the chest pain triage (CPT) model, logistic regression was done using the primary outcome as the dependent variable and potential covariates comprised of vital signs, ECG parameters (ST-elevation, ST-depression, T-wave inversion, Q-waves), troponin, and HRV measures (time, frequency, non-linear). Current triage methods at our institution and modified early warning score (MEWS) were used as comparators.

Results: A total of 797 patients were included for final analysis of which 146 patients (18.3%) met the primary outcome. Patients were an average age of 60 years old, 68% male, and 56% triaged to the most acute category. The model consisted of five parameters: pain score, ST-elevation, ST-depression, detrended fluctuation analysis (DFA) α1, and troponin. CPT model >0.09, CPT model >0.15, current triage methods, and MEWS ≥2 had sensitivities of 86%, 74%, 75%, and 23%, respectively, and specificities of 45%, 71%, 48%, and 78%, respectively. The c-statistics of the CPT model, current triage methods, and MEWS for the primary outcome were 0.78, 0.62, and 0.50, respectively.

Conclusions: A predictive chest pain triage model using multiple variables including HRV, vital signs, ECG, and troponin may be more effective in accurately triaging chest pain patients than current methods. A faster and more accurate triage tool for ED chest pain patients has the potential to vastly improve efficiency and allocate resources to the patients who need the most care.
Extracorporeal Membrane Oxygenation in Premature Infants

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**Background:** For infants with cardiopulmonary failure, extracorporeal membrane oxygenation (ECMO) can be lifesaving. Traditionally limited to term infants, ECMO is increasingly used in premature infants with unknown benefit. The aim of this study was to characterize the association between infant characteristics and ECMO survival.

**Methods:** We performed a retrospective cohort study. We included infants without major congenital anomalies supported with ECMO prior to discharge from a Pediatrix Medical Group neonatal intensive care unit from 1998-2013. We used multivariable logistic regression to evaluate associations between infant characteristics and survival to discharge.

**Results:** We identified 275 infants, of which 52 (19%) were <37 weeks gestational age (GA). Median GA, birth weight, and postnatal age at ECMO initiation were 39 weeks (25th, 75th percentile 37, 40), 3199 g (2830, 3605), and 2 days (1, 3). Median ECMO duration was 6 days (4, 8), and 61% of ECMO support was veno-venous. The most common diagnoses were persistent pulmonary hypertension of the newborn (89%) and meconium aspiration syndrome (39%). Bronchopulmonary dysplasia (17%) and intraventricular hemorrhage (6%) were the most common morbidities. Overall survival to discharge was 87%, but was lower in premature compared to term infants, 77% vs. 89%, p=0.02. In multivariable analysis, acute kidney injury [odds ratio (OR) 6.36 (95% CI 1.90, 21.33)], postnatal age at cannulation [OR 5.91 (1.42-24.54)], and prematurity [OR 2.45 (1.01, 5.98)] were associated with lower survival.

**Conclusions:** Prematurity, postnatal age, and acute kidney injury were associated with lower ECMO survival. Future studies are needed to identify risk factors and strategies to improve survival in premature infants supported with ECMO.
Adoption Factors and Usage Patterns of Vendor-Supplied Mobile Applications for Interaction with the Electronic Health Record
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Dean’s Merit Scholarship, MMCi Program Scholarship, Dual Degree Scholarship

Background: The use of mobile technology by providers has continued to rise. An ACGME survey of physicians reported that 85% of respondents used a smartphone. Additionally, according to a 2014 HIMSS Analytics study on mobile devices, 54.7 percent of respondents used smartphones to access patient information. Mobile technologies have been shown to improve patient documentation, improve decision-making in patient care, give earlier access to information, enhance work patterns, and increase efficiency. EHR vendors such as Epic have developed and released mobile applications to facilitate interactions between providers and their EHR systems. Epic’s mobile apps are Haiku, developed for smartphones, and Canto, developed for the iPad. These apps allow providers to access patient charts, prescribe medications, write progress notes, respond to clinical messages, and capture clinical photos, among other features. It remains unclear which features of these apps are being used by providers currently, which features impact their workflows, which features are most important to providers, and which factors lead to their adoption by providers.

Methods: A digital survey was sent to 7,143 providers at Duke who had been given clinical access to the Haiku and Canto apps. Providers included attending physicians, residents, medical students, nurses, advanced practice providers, and physical therapists among others. Providers were asked a series of questions regarding adoption and usage of the apps.

Results: We received 738 total responses to the survey for a response rate of 10.3%. Nearly all providers (95%) indicated that they owned and would consider using a device for clinical care. Over half of the providers who responded indicated that they had used one of the mobile apps (425, 58%). Significant differences in agreement to adoption factor statements were found between users and nonusers for all questions. A multivariable logistic regression model determined security, relative advantage, trialability, complexity, quality of design, observability, difficulty of setup, training, workload, and compatibility were significant predictors of adoption, with an overall R² of 0.4528. The apps were used most frequently to search for patients and review notes and results. Reviewing notes and results and capturing clinical images were identified as having the largest impact on workflow. Searching for patients, reviewing notes and results, and capturing clinical images were the most important features for users.

Conclusions: Adoption of vendor-supplied, EHR-specific apps is influenced by a number of factors, including factors specified by the Diffusion of Innovations model, including relative advantage, compatibility, trialability, complexity, and observability, as well as users’ perceptions of information security of the apps, adequacy of training, ease of setup, and quality of design. These factors may be used by information technology developers and by hospitals and health systems to increase uptake and usage of the apps by healthcare providers. These mobile apps are currently most used for reviewing patient data and searching for patients. In addition to these features, providers find the ability to take clinical images to be highly impactful and important.
An Examination of Participation in Youth Programs for Adolescents with Chronic Illness

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Background: Youth with childhood onset chronic illness (COCI) are at risk for low school attendance and poor educational outcomes. In general, youth programs outside of school are associated with positive adult outcomes. This study aimed to describe the engagement of youth with and without COCI in youth programs and identify predictors of participation.

Methods: Healthy participants between 13-18 years old were recruited from a large pediatric primary care practice and participants with COCI were recruited from nine specialty pediatric clinics between August 2013 and March 2015. Univariate and bivariate analyses for program participation were conducted for youth with and without COCI. We performed multivariable logistic regressions to examine predictors of program participation.

Results: Youth with COCI (n=140) and without COCI (n=130) participated in the same types of programs and average number of programs (n=3), except that youth with COCI were more likely to participate in illness-specific programs. In adjusted odds ratios for program participation, COCI was not a significant predictor while Hispanic (AOR: 0.065), Black (AOR=0.28), and ‘other’ race/ethnicity (AOR=0.20) were significant negative predictors of program participation. Youth whose parents had at least a four-year college degree had significantly higher odds of program participation (AOR=5.08).

Conclusions: Adolescents with COCI were just as likely as healthy peers to participate in youth programs. Given high rates of participation by youth with COCI in after-school, religious, sports, and camp programs these programs may be fruitful sites for interventions. For targeted outreach, differences in participation rates were influenced by race/ethnicity and parental education level.
**Evidence implicating distinct FGF13 Isoforms in a human epilepsy syndrome**

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**Background:** GEFS+ is a genetic epilepsy syndrome with heterogeneous clinical phenotypes including febrile seizures (FS), focal and generalized epilepsies and severe epileptic encephalopathies. Mutations causing GEFS+ have been identified in four different genes in large pedigrees, collectively accounting for less than 20 percent of cases. Our lab identified a family with a translocation between chromosomes X and 14 that is associated with a GEFS+ phenotype. The breakpoint on the X chromosome disrupts a gene encoding FGF13, an auxiliary protein of voltage gated sodium channels. *Fgf13* encodes five isoforms: S, U, Y, V and VY. The translocation eliminated the expression of three (V, Y, and VY) isoforms, but preserved expression of two (S and U) isoforms. Our lab engineered a mouse model eliminating all isoforms of FGF13, which resulted in embryonic lethality in males. The heterozygous females exhibited features of the GEFS+ phenotype, which implicates disruption of *Fgf13* as the cause of the nuclear family’s phenotype.

**Methods:** In order to understand the role of individual isoforms of FGF13 in causing GEFS+, we engineered another mouse line by selectively deleting exon 1Y of *Fgf13*, which eliminates isoforms Y and VY but preserves isoforms V, S, and U. To mimic febrile seizures, animals were subjected to hyperthermia.

**Results:** In sharp contrast to the embryonic lethality of males lacking all isoforms of *Fgf13*, exon Y null males had normal lifespans. Age-dependent hyperthermia-induced seizures were evident in Y null and heterozygous mutant mice but not in wild type control mice.

**Conclusion:** Our findings demonstrate that deletion of exon 1Y is sufficient to reproduce a key facet of the GEFS+ phenotype, namely hyperthermia-induced seizures seen in the nuclear family. This implies that elimination of isoforms Y and/or VY is sufficient to cause this facet of the GEFS+ phenotype. Additional characterization of these phenotypes is ongoing. Our results guide molecular genetic analyses of GEFS+ cases and shed light on the functional significance of distinct FGF13 isoforms as well as mechanisms of epileptogenesis.
Underwater blast injury: A systematic review of patterns of trauma

Luke Stalcup, Rachel M. Lance MS, Cameron Bass PhD

**Background:** While it has long been known that people suffer physical trauma from explosions that occur underwater, there exists little quantitative analysis of the medical patterns of this trauma or how these injuries are most likely to present clinically. Recently, injury risk analyses were published that described the blast exposure levels required for the creation of serious injuries, but these analyses did not investigate the clinical patterns of the injuries themselves beyond a basic division into the pulmonary and gastrointestinal systems. The goal of this study was to systematically review the patterns of trauma on a finer scale from reported cases, and to develop a quantitative assessment of the risks of specific injury types from underwater explosions.

**Methods:** A total of 135 records were examined, all describing blast injuries from underwater explosions. Of these, 105 contained sufficient clinical information on specific cases to warrant inclusion in the study, and 33 records contained sufficient information to perform complete computational reconstructions to determine blast exposure. Within these 33 records were reports covering 90 individuals exposed to levels of blast sufficient that they caused documented injuries. The documentation of these injuries was reviewed and specific injury types were counted as either present or absent. Sixteen specific types of physical exam findings were identified based on preliminary review of the records. Twenty-four types of physical injury were also identified. Some types of injury were included for completeness, since they seemed likely to occur in the context of the other injuries listed. The records were reviewed thoroughly and the number of occurrences of each injury type was counted for all patients, and well as the number of instances of a positive physical exam finding. A chi-squared analysis was conducted to identify the relationship between the patterns of injuries categorized by exposure levels.

**Results:** The observed injuries were more frequently to the abdomen, though lung injuries were noted. Among injuries to the abdomen, the most frequent were those to the ileum and cecum. The rest of the bowel was injured much less frequently in this study. The clinical picture is one of possible peritonitis, rigid abdomen, tachycardia, and shock-like features. Beyond this, the clinical picture is one of traumatic injury. $\chi^2$ value for lung injuries was 6.1 with 2 degrees of freedom. $\chi^2$ value for abdominal injuries was 26 with 6 degrees of freedom. These results imply that higher blast exposure leads to more types of injury ($p < 0.05$, $p < 0.005$ respectively).

**Conclusions:** The clear result of this study is that the patterns of injury observable from underwater blast include predominantly injuries to the small bowel, but also to the lungs. Among injuries to the bowel, the ileocecal region seems to suffer the most. In all cases, a clear clinical picture of traumatic injury was present. With respect to the probable mechanisms of injury this study gives some support to the theory that shear waves propagating though the tissues as well as spalling effects on tissues are what leads to the injurious effects observed in these reports.
Should Physicians Take Societal Cost Into Consideration?

Alissa Stavig, BS, John D. Yoon, MD, Farr A. Curlin, MD

**Background:** Prior studies suggest U.S. physicians believe they are obligated to help contain health care costs but also to do what is best for their patient no matter the cost. The purpose of this study is to examine whether physicians believe they should pay attention to societal cost only with respect to interventions that will have little clinical benefit.

**Methods:** Analysis of data from a 2010 mailed survey of 1156 U.S. physicians was performed. Criterion measures were physicians agreement or disagreement with two statements: 1) “Doctors should not consider the societal cost of medical care when caring for individual patients,” and 2) “Doctors should refuse requests from patients or their families for costly interventions that have little chance of benefiting the patient.”

**Results:** Response rate was 62%; 47% of physicians agreed that physicians should not consider the societal cost of medical care when caring for individual patients, whereas 69% agreed that physicians should refuse requests for costly interventions of little benefit. Physicians who care for critically ill patients, or who are in specialties that care for more patients at the end of life, were more supportive of refusing costly, non-beneficial interventions.

**Conclusion:** This study provides some evidence that insofar as physicians believe they should help control societal costs, they believe they should do so primarily by refusing costly non-beneficial interventions.
Subfoveal choroidal thickness and associated changes in women with severe preeclampsia

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Background: Preeclampsia is a multi-system disease of pregnancy characterized by new onset hypertension with proteinuria or end-organ dysfunction after 20 weeks of gestation. It occurs in approximately 3.4% of pregnancies in the United states. One defining feature of preeclampsia with severe features is new onset visual disturbance, which can include obscuration, photopsia, scotoma, or visual loss. Given the unique accessibility of the choroid to high-resolution, non-invasive imaging, several studies have sought to identify changes in this structure’s thickness. However, the findings from these studies have been mixed regarding whether or not the choroid thickens in women with preeclampsia as compared with normotensive controls and/or non-pregnant women. Knowing that evidence for this change was equivocal, our group was interested in exploring how subfoveal choroidal thickness (SFCT) differed between women with severe preeclampsia and those with normotensive pregnancies, and to investigate correlations between such imaging findings and other potentially mechanistic indicators and biomarkers of the change, such as maximum blood pressure, gestational age at delivery, soluble fms-like tyrosine kinase (sFlt-1), placental growth factor (PIGF), soluble endoglin (sEng) levels, and color Doppler imaging (CDI) indices from ophthalmic artery ultrasound.

Methods: This was an incident case-control study based on two groups of postpartum women matched by ethnicity and parity: 37 women diagnosed with preeclampsia with severe features (sPE) and 39 normotensive controls. All subjects underwent enhanced depth imaging spectral-domain optical coherence tomography (EDI SD-OCT) and blood draw for serum analysis. A later subset of patients from each of the two study groups additionally participated in a CDI study of their ophthalmic artery, where resistivity index (RI) and peak ratio (PR) were recorded. A final subset of patients from each study group was also imaged by an AngioPlex OCT for angiographic imaging of the choroid.

Results: Cases with sPE demonstrated no change in SFCT compared to controls. Amongst cases, SFCT and gestational age at delivery (GA) were related in an inverse fashion ($r^2 = 0.26, P = 0.002$). sFlt-1, sEng, and sFlt-1:PIGF ratio were increased amongst cases ($P = 0.0016, P = 0.0062$), while PIGF levels were not different across groups. There was a significant positive association of PIGF with SFCT amongst cases ($r^2 = 0.3, P = 0.0024$), while no significant correlation was found between sFlt-1, sEng, or sFlt-1:PIGF ratio and SFCT in either group. Average PR and RI in cases and controls was $0.73 \pm 0.14$ and $0.57 \pm 0.07$ ($P = 0.1272$) and $0.74 \pm 0.07$ and $0.79 \pm 0.06$ for ($P = 0.2672$), respectively. Neither PR nor RI was significantly associated with SFCT across groups ($r^2 = 0.2950, P = 0.2654, r^2 = 0.6223, P = 0.0622$). No qualitative differences in OCT-angiography imaging of choroid was discovered between groups.

Conclusions: We show there is a relationship between the degree of disease severity, as measured by GA at delivery, and the presence and severity of choroidal thickening. We also show an association between this ophthalmic imaging index and other, more systemic, derangements associated with preeclampsia, namely PIGF level and RI of the ophthalmic artery.
**Background:** Leo Kanner, in describing autism, also constructed an associated image of cold intellectual parents. There are two popular theories to explain how Kanner arrived at this stereotype, both of which describe a bias present in Kanner's analysis. The referral bias theory suggests that intellectual parents from far away were more likely to be referred to Kanner, whereas the interpretive bias theory suggests Kanner applied his new diagnosis only when parents met his stereotype. This paper is the first to systematically analyze medical records from Leo Kanner’s clinic to elucidate the extent to which these forms of bias can explain Kanner's autism parent stereotype. In line with recent work, we have situated our analysis within the context of childhood schizophrenia, from which autism emerged.

**Methods:** We performed a literature review directed at all of Kanner’s published work between 1935-1955, as well as the American literature relevant to childhood schizophrenia from the same time period. Kanner’s unpublished papers at the American Psychiatric Association and Johns Hopkins were also consulted. We ordered a series of medical records of children with a diagnosis of autism or childhood schizophrenia seen at Kanner’s clinic between 1938 and 1949. We abstracted these medical records by recording patient biographic and demographic information, as well as parental data concerning occupation and educational level. We quantitatively compared the two diagnoses on referral distance and parental education, before turning to a qualitative analysis of the medical records and Kanner's publications.

**Results:** We found that the childhood schizophrenia and autism groups did not significantly differ based on referral distance, paternal education, or maternal education. However, the education categories did show an insignificant trend towards more highly educated parents in the autism group. Thus, while we were able to refute the referral bias theory, the role interpretive bias played is more unclear. It is evident that Kanner, while he may have exaggerated, did not completely fabricate his claims about parental intelligence. Our qualitative analysis of the medical records and his publications suggests that Kanner was experiencing a *publication bias*, which may be thought of as interpretive bias at the level of publication, rather than during diagnosis.

**Conclusions:** When evidence emerged that contradicted Kanner’s parental stereotype, he could not let go of his idea, and he continued to present his patients’ parents in his published work in a way that supported his initial construction. Additionally, the ambiguity that existed between childhood schizophrenia and autism gave him ample latitude to make sweeping generalizations about his supposedly distinct autistic children—if a child or the parents did not fit his construction, he could simply utilize the childhood schizophrenia diagnosis as an alternative. Understanding how Kanner arrived at his classic archetype of the autism parent bears relevance because that very stereotype led autistic children from families of lower socioeconomic status to not be recognized for a generation.
Characterizing pulse deficits in atrial fibrillation using simple ECG features

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Background: Atrial fibrillation is characterized by irregular intervals, which can manifest as pulse deficits, or absence of a pulse wave following ventricular depolarization. We sought to characterize pulse deficits based on ECG features and correlate presence of pulse deficits with clinical characteristics, such as symptom severity and findings on cardiac imaging.

Methods: Data was collected from 100 patients having radiofrequency ablation. For each patient, two 60s epochs of 12-lead surface ECG and radial intra-arterial blood pressure (IABP) were extracted at random time periods when patient was in AF rhythm. RR intervals (RRI) were calculated in Lead I using Pan-Tompkins algorithm. A novel algorithm was developed and using IABP, identified pulse deficits as a wave with pulse pressure < 20% mean pulse pressure. The preceding RRI was defined as S, and the pre-preceding RRI was defined as L. Patients were classified based on presence or absence of pulse deficits. For patients with pulse deficits, additional RRIs associated with normal pulses (L' and S') were calculated. ECG features in pulse deficits and normal pulses were compared, and univariable and multivariable logistic regression were used to assess detection capabilities of these features. In addition, patients with and without pulse deficits were compared on symptom severity, based on Canadian Cardiovascular Society AF Score and Mayo Symptom Severity Index, and on cardiac MRI findings, such as evidence of LVH, atrial abnormalities, or valvular dysfunction.

Results: Eighteen patients had pulse deficits while 26 patients had none. In total, 628 pulse deficits were observed with L (621±194ms) greater than S (438±54.5ms) (p <0.0001). L and S were both lower in pulse deficits than L’ and S’ in normal pulses (p < 0.001), respectively; however, the percent decrease from L to S was greater in pulse deficits than from L’ to S’ in normal pulses (p < 0.001). S produced the most accurate univariable logistic regression model (c-statistic 0.80). Using L and S in multivariable logistic regression produced the most accurate model (c-statistic 0.83). CCS AF score was higher in patients with pulse deficits (2.50 v. 2.33), but difference was not significant (p = 0.81). Patients did not differ in total Mayo AF Symptom Severity Inventory (p = 0.83). Patients with PDs had slightly higher scores for Lightheadedness (1.25 v. 0.81) and Shortness of Breath (2.25 v. 1.87), but both were not statistically significant (p = 0.33, 0.58, respectively). Patients with pulse deficits were more likely to have mitral regurgitation (0.33 v. 0.12) with near significance (p = 0.09).

Conclusion: This study demonstrates that it is possible to detect hemodynamic phenomenon, such as pulse deficits, using simple ECG features. We developed a logistic regression model with high accuracy and based solely on two preceding RRIs. Given small sample size, we were not able to draw conclusions regarding the clinical significance of having pulse deficits, but patients with mitral valve regurgitation seem more likely to also have pulse deficits. Further work is needed to assess clinical significance and to develop a realistic model that can be deployed in ambulatory monitoring.
Determining the Prognostic Value of Cardiac MRI for Patients with Elevated Cardiac Troponins and No Significant Coronary Artery Disease

Zachary Walker, Han W Kim, Michele Parker, Raymond J Kim

**Background:** Up to 10% of patients with suspected ACS who undergo cardiac catheterization for potential percutaneous coronary intervention are found to have insignificant coronary artery disease. There are a number of cardiac pathologies including, myo/pericarditis, takotsubo cardiomyopathy, acute myocardial infarction with recanalization, as well as others that can present with elevated cardiac troponins in the absence of obstructive CAD. Prior cardiac MRI (CMR) studies looking at this population have reported variable prevalences of the most common diagnoses for these patients. Furthermore, no studies have been able to make substantial conclusions about the prognosis of this population, mostly due to limited follow-up data and sample size. As such, the aims of this study were two-fold: (1) to determine rates of the cardiac pathologies in a larger patient population presenting with positive cardiac troponins and nonobstructive CAD and (2) to determine if any prognostic information is gained based on pattern and/or extent of gadolinium hyperenhancement (HE) present in these patients.

**Methods:** 172 consecutive patients (mean age: 55 ± 16) presenting with positive serum troponins, nonobstructive CAD (≤50% stenosis) by x-ray coronary angiography, who were then referred for CMR were enrolled in the study. Patients underwent cardiac MR imaging consisting of cine imaging and delayed enhancement, which were used by experts to determined patterns and severity of HE as well as a final diagnosis. Patients were followed for major adverse cardiac events (MACE: acute MI, CVA, death, Hrt transplant) in addition to some soft cardiac events.

**Results:** HE was present in 96 patients (55.6%). CMR provided a diagnosis in 125 of 172 patients (73%). Based on HE patterns, 41 patients (24%) were diagnosed with acute MI; 40 patients (23%) were diagnosed with non-ischemic cardiomyopathy (NICM); and 23 patients (13%) were diagnosed with myocarditis. Other less-prevalent diagnoses included hypertrophic cardiomyopathy (5%) and takotsubo cardiomyopathy (3%). The median follow up for MACE was 46 months (interquartile range 7-89) in 172 patients. 72 patients (42%) experienced a MACE during follow-up. Of those, 61 patients (35% of total patients) died during follow-up. Preliminary analysis shows that death rate was not significantly \( P \) value 0.88) related to the presence of HE on initial CMR scan over approximately 12 years. Additionally patients with HE were no more likely to have an MI during follow up than those without HE \( P \) value 0.46). Interestingly for patients who had an ICD implanted during follow-up, the presence of HE was significantly associated \( P \) value 0.04) with a greater number of appropriate ICD shocks delivered.

**Conclusion:** In patients with positive cardiac troponins and nonobstructive CAD, cardiac MRI has a clear diagnostic role. Preliminary analysis of follow-up data suggests that HE may be correlated with some cardiac-related events, however, further analysis regarding the specific patterns of HE and the burden of HE with respect to MACE and other soft events needs to be finished in order to make a conclusive statement about CMR’s prognostic value in this population.
Using Hyperpolarized $^{129}$Xe MRI to Visualize and Quantify Gas Transfer in Idiopathic Pulmonary Fibrosis

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**Background:** Idiopathic pulmonary fibrosis (IPF) is a devastating form of interstitial lung disease with an estimated survival of 2-3 years following diagnosis. With the recent approval of 2 drugs to treat IPF and additional drugs in development, there is a pressing need to detect therapy response or worsening function more rapidly than is possible using forced vital capacity (FVC). A promising approach is to use hyperpolarized xenon gas MRI to quantify gas exchange 3-dimensionally. Upon inhalation, gas-phase xenon diffuses into interstitial barrier tissues, plasma, and RBCs. In each compartment, $^{129}$Xe exhibits a distinct resonance frequency enabling imaging of its distribution in a single breath. In IPF, increased interstitial fibrosis enhances xenon transfer from alveoli to barrier tissues, and diminishes transfer to RBCs. Here, we demonstrate ways to quantify gas transfer images into maps that depict functional changes in IPF. Our objectives are to establish their correlations with metrics from pulmonary function tests, validate that images of impaired gas transfer are consistent with known patterns of disease, and identify image signatures that predict progression.

**Methods:** After completing pulmonary function testing, 13 healthy individuals (33.6 ± 15.7 yrs) and 12 patients with IPF (66.1 ± 6.3 yrs) underwent $^{129}$Xe MRI studies to generate 3D images of $^{129}$Xe in gas and dissolved-phases. Dissolved $^{129}$Xe was separated into RBC and barrier images using a 1-point Dixon method. Quantitative gas transfer maps were created by dividing $^{129}$Xe signal in barrier and RBC compartments by gas signal in each voxel and binning them based on the distribution derived from normal subjects. Barrier:gas and RBC:gas maps were qualitatively compared to CT, while their mean values were correlated with pulmonary function testing. For each map, gradients were calculated in the anterior/posterior, apical/basal, and central/peripheral directions. Two IPF subjects were followed longitudinally to illustrate disease progression following initiation of anti-fibrotic medications.

**Results:** Both barrier:gas and RBC:gas were strongly correlated with DL$_{CO}$ ($r^2 = 0.56$, $p < 0.001$ and $r^2 = 0.49$, $p < 0.001$, respectively), while RBC:barrier correlated most strongly with DL$_{CO}$ ($r^2 = 0.87$, $p < 0.001$). IPF subjects exhibited significant gas transfer impairment, illustrated by reduced RBC:gas in the basal (33%, $p = 0.023$) and sub-pleural (17%, $p < 0.001$) lung compared with controls. Barrier signal was increased by 194% throughout the lung. Our imaging-derived metrics could distinguish between the clinical trajectories in 2 IPF subjects.

**Conclusions:** This promising functional imaging modality, safe and well tolerated, is a powerful tool for understanding the pathophysiology of IPF, and may ultimately be used in conjunction with CT imaging and PFTs in the diagnostic work-up and clinical decision-making for patients.
Long-term Furosemide Exposure Does Not Increase Risk of Abnormal Newborn Hearing Screen in Premature Infants

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Background: Bronchopulmonary dysplasia (BPD) is one of the most common complications associated with preterm birth and is the leading cause of pulmonary morbidity in premature infants. Additionally, BPD can lead to long-term growth and neurodevelopmental impairment. Furosemide is a diuretic that is commonly used in premature infants for the prevention and management of BPD. However, the risk of hearing loss in infants exposed to furosemide for prolonged periods is unknown. The purpose of this study was to evaluate the association between long-term furosemide exposure for ≥28 days and abnormal hearing screen results in premature infants.

Methods: We examined a cohort of infants <1250 g birth weight and <30 weeks gestational age with recorded hearing screen results who were discharged home from 210 neonatal intensive care units between 2004-2013. We excluded infants exposed to 1-27 days of furosemide. We collected demographic, medication, and other clinical data, discharge data, and respiratory support information. Additionally, we collected data on risk factors for hearing loss including cytomegalovirus (CMV) infection, vancomycin exposure, gentamicin exposure, and serum bilirubin levels >15 mg/dL. Using propensity scores for exposure to furosemide, infants exposed to furosemide for ≥28 days were matched 1:1 with replacement to infants who had never been exposed to furosemide. The matched sample was then used to estimate the percent increase in the risk of an abnormal hearing screen result in the exposed group due to prolonged furosemide exposure for ≥28 days.

Results: We identified 1020 infants who had been exposed to furosemide for ≥28 days and 12,900 infants who had never been exposed to furosemide. The infants exposed to furosemide for ≥28 days were matched to 901 subjects without furosemide exposure. After adjusting for covariates, the risk of abnormal hearing screen in the furosemide-exposed group was not significantly increased, 2.5% (95% CI: -0.85,5.59), P=0.15, compared to the never-exposed group.

Conclusions: Long-term furosemide exposure ≥28 days was not associated with an increased risk for abnormal hearing screen results in premature infants. The findings from our study have important implications for understanding the safety of furosemide in premature infants and can provide a basis for the development of future trials to evaluate safety and efficacy. Additional studies with extended audiology follow-up will be needed to evaluate furosemide safety prospectively.
An internally randomized control trial of radiation exposure using ultra-low radiation imaging (ULRI) versus traditional C-arm fluoroscopy for patients undergoing single-level minimally invasive transforaminal lumbar interbody fusion (TLIF)

Timothy Y. Wang

Background: Minimally invasive transforaminal lumbar interbody fusion (MIS TLIF) is an increasingly popular approach to lumbar spine fusion. Compared to the traditional open approach, MIS TLIF has multiple benefits including decreased blood loss, shortened recovery times, and reduced analgesic requirements. Nevertheless, this approach comes with an increased reliance on intraoperative image guidance, most commonly through fluoroscopy, which continues to remain a necessity for confirming anatomic positioning, guiding implant and graft placement, as well as assessing spinal alignment. This results in a significant increase in radiation exposure to surgeon and operating room (OR) personnel, which has detrimental short and long-term health effects. Our goal with this work was to see if by using ultra-low dose radiation settings coupled with image enhancement, this exposure could be minimized.

Methods: An IRB approved, prospective, internally randomized controlled trial was performed comparing ultra-low dose settings coupled with image enhancement software to conventional fluoroscopic imaging. Inclusion criteria included 1) Patients ≥ 18 years of age, 2) undergoing single level MIS-TLIF from August 2015 through February 2016. In this study, each patient served as their own control, randomly assigning one side of MIS-TLIF for cannulation and k-wire placement using each imaging modality. Further, the case was also randomly divided into screw placement and cage placement/final images to allow further comparisons amongst patients. Radiation production from the c-arm fluoroscope as well as radiation exposure to all operating room personnel were recorded. Time spent on each interval was also recorded.

Results: 24 patients met inclusion criteria and were then randomly assigned to undergo a single level MIS-TLIF. In no case was low radiation imaging abandoned, and no patient experienced neurologic decline or required hardware repositioning. Everyone in the operating room: the physician, scrub nurse, circulator, and anesthesiologist, all benefited with 61.6-83.5% reduction in radiation exposure during cannulation and k-wire placement using each imaging modality. In every case but the anesthesiologist dose, this was statistically significant (p<0.05). This benefit did not result in increased procedural time (p = 0.78).

Conclusion: Ultra-low radiation imaging, when aided by image enhancement software, affords the ability for all parties in the operating room to substantially decrease their radiation exposure compared to standard-dose c-arm fluoroscopy without adding additional time or an increased complication rate.
Longitudinal reproducibility of optical coherence tomography in children with physiologic cupping and stable glaucoma

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Background: With its ability to provide cross-sectional views of the retina, spectral domain optical coherence tomography (SD-OCT) has become an integral component of the eye examination in adult patients. To capture this image, the patient must sit upright at a stationary table-top machine and fixate his or her vision to a specified target. Motion artifacts make processing the images, called “segmentation,” difficult. In children, this image acquisition process is particularly challenging. Depending on the age of the child, obtaining his or her cooperation with the imaging process may be impossible. Previous studies using Spectralis (Heidelberg, Germany) SD-OCT have shown good reproducibility for measurements of both peripapillary retinal nerve fiber layer (pRNFL) and macular thicknesses in eyes of adults with known or suspected glaucoma. However, there are few studies which validate the measurements acquired from the SD-OCT scans in children and ensure that they are reproducible on multiple repeat imaging sessions and can be relied upon in actual clinical practice. In particular, for children with glaucoma, reproducible measurements are essential to confirm that thinning detected on SD-OCT imaging corresponds to true thinning of the retina caused by increased pressure due to disease progression. As a result, measurements obtained by SD-OCT imaging carry clinical significance in guiding management decisions.

Methods: This retrospective study included 47 eyes of 47 children (age <18yrs) with physiologic cupping (clinically diagnosed), stable primary congenital glaucoma (PCG), and juvenile open-angle glaucoma (JOAG) having had ≥2 SD-OCT studies over >1-year period. Thicknesses of average pRNFL and six individual sectors, as well as volumes of 3 segmented retinal layers and total retina were measured. Spectralis review software was used for segmentation. Intraclass correlation coefficients (ICC) and coefficient of variation (COV) were calculated for each of the above OCT measurements.

Results: 16 eyes with physiologic cupping, 20 with PCG, and 11 with JOAG were included. For physiologic cupping, PCG, and JOAG, mean(±SD) ages at initial SD-OCT imaging were 11.0±3.3, 9.7±3.3, and 13.3±2.0 years, respectively; mean times between first and last SD-OCTs were 2.1±1.1, 3.0±1.4, and 2.8±1.6 years, respectively. ICCs for the average and sectoral RNFL thicknesses across three visits were 0.887-0.997 for all groups. ICCs for segmented retinal layer volumes were 0.806-0.993 for all groups. ICCs for total retinal volume for physiologic cupping, PCG, and JOAG were 0.993, 0.954, and 0.988, respectively. COVs for average pRNFL thickness were 1.2%, 1.7%, and 2.6% for physiologic cupping, PCG, and JOAG, respectively. For all other measurements, COV ranged from 0.4-6.7%.

Conclusions: Reproducibility of longitudinal SD-OCT measurements for average pRNFL thickness in children with physiologic cupping and stable glaucoma over ~2 years is comparable to short-term reproducibility (COV) in normal children (1.16%) and normal and glaucoma adults (1.62-3.4%).
Management of Infertility in Women with PCOS

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**Background:** Polycystic Ovary Syndrome (PCOS) is a heterogeneous endocrine disorder that is often characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovaries. The prevalence of this disease in reproductive age women ranges from 4-19.9% according to the clinical diagnostic criteria implemented. Infertility affects 40% of women with PCOS and the disease is the leading cause of anovulatory infertility. The poor fecundity of these women is also associated with increased early pregnancy loss and later pregnancy complications. According to the latest ACOG practice bulletin, there are no evidence-based schemas to guide the initial and subsequent choices of ovulation induction in women with PCOS.

**Methods:** We conducted a systematic review on studies conducted in adults and published from January 1, 2007 to present using MEDLINE, PubMed®, Embase®, and the Cochrane Database of Systematic Reviews. We abstracted data on age, BMI, race, interventions and comparators, and the outcomes of live birth, pregnancies, pregnancy complications, neonatal outcomes, time to pregnancy, quality of life, cost, and short- and long-term maternal and child adverse effects after treatment.

**Results:** We identified 32 studies, 30 RCTs and 2 observational studies that met our inclusion criteria. We found the following: Clomiphene citrate results in higher birth rates than metformin alone as first-line therapy. The combination of metformin and clomiphene may improve live birth rates in women with higher BMI, but precision is limited. Letrozole has higher live birth rates than clomiphene alone, with no increase in multiple birth rates, ectopic pregnancy, or miscarriage. Surgical management with laparoscopic ovarian drilling does not improve outcomes compared to oral ovulation agents. Use of gonadotropins as primary therapy does not improve outcomes compared to oral agents. Pretreatment with metformin prior to ART may improve live birth rates and decrease ovarian hyperstimulation syndrome. Use of GnRH antagonists as part of the controlled ovarian hyperstimulation protocol in IVF/ICSI reduces the incidence of OHSS compared to GnRH agonists.

**Conclusions:** The overall strength of evidence was low. The results align with what has been written previously on this topic. However, we found many inconsistencies in estimates of the effect of interventions and found study design limitations that negatively impacted bias. Many studies did not report live birth as an outcome and ART studies often did not include results per diagnosis. Additionally, our subpopulations of race and BMI were rarely addressed in the literature. Considering that PCOS is associated with weight gain and that health disparities are a known issue in medicine, these subpopulations need to be focused on.
**Exercise-Induced Cartilage Strain at the Shoulder: A Study in vivo**

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**Background:** Glenohumeral cartilage is critical in normal shoulder kinematics, which may be disrupted in osteoarthritis. Although many shoulder injuries occur during sport or exercise, the effect of significant loading on the glenohumeral joint are yet to be wholly described. This study sought to clarify the effect of exercise on the shoulder by directly measuring glenohumeral cartilage strains.

**Methods:** In this IRB-approved study, 10 healthy subjects (7 male, 3 female; mean age: 26 years, range: 22-28 years) without history of shoulder complaints underwent exercise testing via a series of 30 pushups, performed according to defined form. Before and after exercise, axial MRI was taken of the dominant shoulder (Truefisp, Siemans) to visualize the glenohumeral cartilages. Prior to their visit, subjects refrained from heavy lifting/exercise and rested immediately before pre-exercise imaging. Pre- and post-exercise MR images were imported into solid modeling software (Rhinoceros; Robert McNeel and Associates), and bony and cartilage surfaces of the humeral head and glenoid were traced. All tracings were reviewed for accuracy by a musculoskeletal radiologist. Cartilage thickness maps were generated for both pre- and post-exercise models by calculating cartilage thickness as the nearest distance between cartilage and bone surfaces. After registration of the pre- and post-exercise models, cartilage strain (% change in thickness) was sampled at 18 sites on the humeral head and 9 sites on the glenoid. Overall humeral and glenoid strains were calculated as averages of all respective samples. Statistical significance of strain and cartilage thickness measurements was assessed using student’s t-test, ANOVA, and Mann-Whitney U test.

**Results:** Significant compressive strains were detected in both the humeral head (17% ± 9%) and glenoid (15% ± 9.6%) cartilages as a result of pushups (p<0.0001). Pre-exercise, humeral cartilage averaged 1.0 mm (± 0.06 mm), and glenoid cartilage 1.3 mm (± 0.06 mm). Of note, average baseline humeral cartilage was thinner in female subjects (0.92 mm) than in the male subjects (1.0 mm; p<0.001). Average strain after pushups in the anterior glenoid (19% ± 1%) was significantly greater than those in the central (15% ± 2%) or posterior (12% ± 2%) regions (p=0.006). There was no difference in glenoid strains superiorly-inferiorly (p=0.76). Regional average strains in the humeral head did not show significant differences either in the anterior-posterior (p=0.07) or superior-inferior (p=0.06) axes. No strain differences were found between male and female subjects. Two subjects were excluded from analysis due to asymptomatic labral/cartilage defects found during imaging review.

**Conclusion:** Common intensive upper-extremity exercises such as pushups induce significant cartilage strains at the glenohumeral joint. These data taken from direct measures of the shoulder suggest that with pushups, the humeral and glenoid cartilages undergo strains that may be comparable to, if not exceed, those seen in the knee and ankle during exercise.
Creating a biomarker burden and strength index to link serum metabolites and inflammatory marker levels with functional status of older adults with varying health conditions

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Background: The human aging process is associated with increased level of inflammation, mitochondrial dysfunction and other dysregulated metabolic systems, each of which has an effect on circulating serum markers of inflammation and metabolism. A previous researcher at Duke has found that individually, high levels of markers such as Interleukin-6 (IL-6), D-Dimer and acylcarnitine factor (developed from circulating acylcarnitines) are associated with worse physical performance in older adults. By combining inflammatory and metabolic markers to form an index, we hoped to capture the complex interplay of inflammation and metabolism in age-related changes of physical performance.

Methods: A meta-analysis was performed using a combination of three cross-sectional studies conducted in older adults with different health backgrounds. Each marker was individually correlated with usual gait speed, a measurement for physical performance in older adults, and was assigned a burden or strength score of one. The index was developed from the cumulative scores using step-wise regression.

Results: Two biomarker indices were developed from twenty inflammatory and metabolic markers to correlate with better and worse physical performance in older adults. Preliminary results show that twelve markers contained information particularly relevant to predicting worse physical performance and were used to build a model that demonstrated steady, step-wise decline in outcome with each added biomarker burden. Similarly, eight markers with a cumulative effect of markers associated with better physical performance formed another index for which there was a step-wise increment in physical performance in the same population.

Conclusion: The biomarker indices predict physical performance better than individual markers and are the first of such indices to link multiple inflammatory/metabolic markers with physical performance in older adults. They shed light on the complicated systemic processes that may lead to physical performance decline, or if markers lie on the other end of the spectrum, may demonstrate resilience to such age-related decline. The indices provide a potential clinical tool to identify patients at risk for, as well as molecular processes most relevant to, such decline that may necessitate clinical intervention.
Precision Medicine in Point-of-Care Management of Surgical Complications
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Abstract—Surgeon experience or population data, rather than personalized predictions, currently guide post-surgical care. We hypothesize that predictive modeling of surgical outcome data at the point-of-care can augment experiential decision-making and thus translate into reduction of post-surgical complications and hospital length of stay. A prototype of an integrated analytical platform was developed for: (1) data intake from an electronic health record, (2) predictive modeling using machine-learning techniques, and (3) deployment of predictions results with personalized interventions.

I. BACKGROUND AND OBJECTIVE
Surgical complications are associated with decreased quality of life, inferior survival, and significant cost increases to the health system [1]. “Expert” opinion and population data currently drive guidelines that attempt to prevent or mitigate post-surgical complications. However, individualized risk profiles are not utilized in selecting specific prophylaxes or preventive therapies, such that preventable complications remain prevalent. Therefore, we constructed a Clinical Analytical Learning Platform for Surgical Outcomes (CALYPSO) as an integrated platform for personalized risk prediction and result delivery.

II. METHODS AND CURRENT PROGRESS
First, using national surgical outcomes data from the National Surgical Quality Improvement Program, we fit initial predictive models using penalized logistic regression methods from 60 clinically relevant predictors. Outcomes of interest include cardiopulmonary, renal and urinary tract, venous thromboembolic, surgical site, and septic complications as well as 30-day mortality. Our model performances for each outcome (c-statistics range 0.78-0.93) are comparable or better than the best existing models published by the American College of Surgeons. Next, we developed a user-interface that incorporates existing data from the electronic health record and estimates an individual patient’s relative and absolute risk profile (Figure 1). Finally, variable selection will allow us to display the most important and modifiable predictors via our user-interface. Each flagged predictor is then linked to a set of accepted best practice interventions that specifically targets the risk factor. Visualizing these individualized risks and interventions at the point-of-care allows clinicians to make data-driven decisions rapidly.

III. FUTURE DIRECTION
We aim to test feasibility and measure the benefit of using CALYPSO in actual practice on a surgical ward. Validation of CALYPSO will support its adoption in daily medical practice, both at our institution and elsewhere. Due to the fact that institutional features can affect individual outcomes, we plan to modify our predictive models using transfer-learning techniques. This will allow us to more heavily weight our own institutional surgical data, while still leveraging the wealth of information from the millions of surgeries recorded in the national dataset. At 6-month intervals we will update the prediction models in order to incorporate our recent institutional surgery outcomes. This ongoing process will allow CALYPSO to learn from local factors and drive future predictions towards more accurate risk profiles over time. We also plan to pursue more sophisticated modeling strategies that better account for the relationships between different classes of surgeries.

REFERENCES

Poster #82