At the University of Chicago, in an atmosphere of interdisciplinary scholarship and discovery, the Pritzker School of Medicine is dedicated to inspiring diverse students of exceptional promise to become leaders and innovators in science and medicine for the betterment of humanity.
68th Annual
Senior Scientific Session
Thursday, May 22, 2014

Oral Presentations
1 PM - 4 PM | Biological Sciences Learning Center - Room 115

Poster Presentations
4 PM - 6:30 PM | Gordon Center for Integrative Science - 3rd Floor Atrium

2014 Session Chair
Vinay Kumar, MBBS, MD, FRCPath
Donald N. Pritzker Professor
Chairman, Department of Pathology

2014 Presentation Judges

Matthew Brady, PhD
Department of Medicine

Juliane Bubeck Wardenburg, MD, PhD
Departments of Pediatrics & Microbiology

Anthony Chang, MD
Department of Pathology

Andrew Davis, MD, MPH
Department of Medicine

Harriet de Wit, PhD
Department of Psychiatry and Behavioral Neuroscience

Lucy Godley, MD, PhD
Department of Medicine

Michael Hernandez, MD
Department of Anesthesia & Critical Care

Gavin Hougham, PhD
Department of Medicine

Elbert Huang, MD, MPH
Department of Medicine

R. Stephanie Huang, PhD
Department of Medicine

Catherine Humikowski, MD
Department of Pediatrics

Scott Hunter, PhD
Department of Psychiatry and Behavioral Neuroscience

Kristen Knutson, PhD
Department of Medicine

Peggy Mason, PhD
Department of Neurobiology

Doriane Miller, MD
Department of Medicine

Mark Musch, PhD
Department of Medicine

Olufunmilayo Olopade, MD
Departments of Medicine & Human Genetics

Navin Pinto, MD
Department of Pediatrics

Valerie Press, MD, MPH
Department of Medicine

Tipu Puri, MD, PhD
Department of Medicine

Mark Ratain, MD
Department of Medicine

Milda Saunders, MD, MPH
Department of Medicine

Larry Thaete, PhD
Department of Obstetrics and Gynecology
NorthShore University HealthSystem

Monica Vela, MD
Department of Medicine

Olga Zaborina, PhD
Department of Surgery
**Welcome & Opening Remarks**

Biological Sciences Learning Center - Room 115

1 PM  
**Kenneth S. Polonsky, MD**  
Executive Vice President for Medical Affairs  
Dean, Division of the Biological Sciences  
Dean, Pritzker School of Medicine  
Richard T. Crane Distinguished Service Professor of Medicine

**Holly J. Humphrey, MD**  
Ralph W. Gerard Professor in Medicine  
Dean for Medical Education

**Vinay Kumar, MBBS, MD, FRCPATH**  
Donald N. Pritzker Professor  
Chairman, Department of Pathology

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**Oral Presentations**

Abstracts on Pages 15-24

1:15 PM  
**Ashwin Kotwal, MS; Mentor: William Dale, MD, PhD**  
Colon Cancer Screening Behavior in a Nationally-Representative Sample of Married Couples: Do Spouses Influence Each Other?

1:30 PM  
**Emily Guhl; Mentor: Sandeep Nathan, MD**  
Lower Socioeconomic Status is an Independent Predictor of Major Adverse Cardiac Events (MACE) and Increased Mortality Post-Percutaneous Intervention in Public Health System Patients

1:45 PM  
**Marie Adachi; Mentor: Vineet Arora, MD, MAPP**  
Bringing to Light Associations Between Pain, Depression and Sleep in Hospitalized Adults

2:00 PM  
**Margaret Distler, PhD; Mentor: Abraham Palmer, PhD**  
The Glyoxalase System Regulates GABA-A Receptors and Anxiety

2:15 PM  
**Karthik Sundaram, PhD; Mentor: Joseph Piccirilli, PhD**  
Prolactin Receptor-Mediated Internalization of Imaging Agents Detects Epithelial Ovarian Cancer with Enhanced Sensitivity and Specificity

2:30 PM  
**Fady Riad; Mentor: Andrew M. Davis, MD, MPH**  
QTc Prolongation at an Academic Medical Center: Quantifying the Risk from Medications

3:00 PM  
**Melissa Mott, PhD; Mentor: Stacie Levine, MD**  
Medical Students as Hospice Volunteers: Reflections on an Early Experiential Training Program in End-of-Life Care Education
Poster Presentations

4:15 PM - 6:30 PM | Gordon Center for Integrative Science - 3rd Floor Atrium

Abstracts on Pages 27-79

4:15 PM

Poster Presentations

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Presentation Judging for the Following Awards

5:45 PM

ORAL PRESENTATIONS

Catherine Dobson Prize
For the best oral presentation given by a student in the area of scientific investigation in clinical or social sciences

Leon O. Jacobson Basic Science Prize (MD/PhD students)
Granted to the MD/PhD student whose basic science research is judged to be the most meritorious from among session participants

Leon O. Jacobson Prize (non-PhD students)
For the best oral presentation given by a non-PhD student in the area of the basic biological sciences

Medical and Biological Sciences Alumni Association Prize
For the best presentation made by a student in the area of Applied Scholarship (Global Health, Community Health, Medical Education, or Quality & Safety)

POSTER PRESENTATIONS

Award for Best Poster Describing Applied Scholarship
Award for Best Poster Describing Scientific Investigation in Basic Sciences
Award for Best Poster Describing Scientific Investigation in Clinical Research or Social Sciences

ORAL OR POSTER PRESENTATIONS

Franklin McLean Medical Student Research Award
Granted to the non-PhD student who has performed the most meritorious research in the medical field

Closing Remarks & Awards Presentation

6:15 PM

Vinay Kumar, MBBS, MD, FRCPPath

Acknowledgments

The program committee acknowledges the contributions of the presenters and the organizers of the event.
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The annual Senior Scientific Session was founded by Dr. Leon Jacobson in 1946 to highlight the caliber of Pritzker student scholarship and the quality of their medical education. Dr. Jacobson, a native of Sims, North Dakota, received a Bachelor of Science degree from North Dakota State University in 1935 and his Medical Doctorate from the University of Chicago in 1939. His professional career—invested entirely at the University of Chicago—included serving as Director of the Argonne Cancer Research Hospital as well as Dean of the Division of Biological Sciences.

In 1942, during his residency at the University of Chicago Hospital, Dr. Jacobson was recognized for his scholarly promise. He was tasked with the responsibility of protecting the health of the staff of the Manhattan Project, chosen for this important position because of his research on the biological effects of radiation, as well as his reputation as one of the first doctors to treat blood disorders with radioactive phosphorus. By the conclusion of the Manhattan Project in 1945, Dr. Jacobson and his staff had pioneered several medical advances, including testing the first forms of chemotherapy used to fight cancer. He was later credited with creating the foundation for bone marrow transplantation and initiating the search for the erythropoietin, a hormone that regulates red blood cell production. Erythropoietin is now the basis for a drug that treats chemotherapy-induced anemia in many cancer patients, a revolutionary treatment in the field of oncology.

The Senior Scientific Session is upheld as an annual tradition. By providing graduating Pritzker students with the opportunity to disseminate their research through oral and poster presentations, the legacy of Dr. Jacobson's commitment to innovation through research continues.
2013-2014 Calvin Fentress Fellowship Recipients

Marie Adachi  
Mentor: Vineet Arora, MD, MAPP

Christopher Chesley  
Mentor: Lainie Ross, MD, PhD

Emily Guhl  
Mentor: Sandeep Nathan, MD

Ashwin Kotwal, MS  
Mentor: William Dale, MD, PhD

Joseph Lamplot  
Mentor: Tong-Chuan He, MD, PhD & Hue Luu, MD

Donald (Bailey) Miles  
Mentor: John Kwon, MD, PhD

Neha Sathe  
Mentor: Marshall Chin, MD, MPH

Madeleine Shapiro  
Mentor: Valerie Press, MD, MPH

Ashley Vachon  
Mentor: David Rubin, MD

David Voce  
Mentor: Bakhtiar Yamini, MD

Wenjing Zong  
Mentor: Erika Claud, MD

2013-2014 John D. Arnold, MD Scientific Research Prize Recipients

Maureen Beederman  
Mentor: Russell Reid, MD, PhD

Vikrant Jagadeesan  
Mentor: Sandeep Nathan, MD

Elizabeth Poli  
Mentor: Olufunmilayo Olopade, MD
2013-2014 JOHN D. ARNOLD, MD
MENTOR AWARD RECIPIENTS

In 2012, a grateful alumnus, Dr. Charles Pak, established the John D. Arnold, MD, Scientific Research Prize. This prize was established in recognition of the impact that his mentor had on his education and future career in research. The Arnold Scientific Research Prize recognizes students whose research accomplishments as medical students are based on ongoing, sustained work with a single faculty mentor. The goal of the Arnold Scientific Research Prize is to provide support for the continuation of the mentoring relationship and collaborative research experience during the student’s fourth year of medical school. As part of the application, students are asked to comment on the contributions that their mentors have made towards their professional growth and development. Mentors of the selected students are honored with the 2013-2014 John D. Arnold, MD, Mentor Award for sustained excellence in mentoring medical students.

This year’s John D. Arnold, MD Mentor Awards are bestowed upon:

Sandeep Nathan, MD
Associate Professor of Medicine

Dr. Sandeep Nathan is a renowned Cardiologist who has expertise in interventional coronary and peripheral vascular procedures. Dr. Nathan is among the few cardiologists with the specialized knowledge and skill to perform transradial angiography and intervention. As a general cardiologist Dr. Nathan treats patients experiencing coronary artery disease, peripheral arterial disease, and risk factors for heart disease. His prolific research is focused on platelet biology, interventional device therapies, and intravascular imaging. Further, Dr. Nathan has scholarly interests in the use of antiplatelet and antithrombotic therapies in the management of acute coronary syndromes and heart attacks. He serves as Associate Professor of Medicine, Director of the Interventional Cardiology Fellowship Program, and Co-Director of the Cardiac Catheterization Laboratory.

Dr. Nathan received the John D. Arnold, MD Mentor Award for his work with fourth year student Vikrant “Vik” Jagadeesan. In their novel work together, Dr. Nathan and Vik investigated the quantitative and compositional differences in coronary atheroma of Acute Coronary Syndromes (ACS) versus non-ACS patients. Vik highly regarded the influence that Dr. Nathan had upon his professional development, as shown through Dr. Nathan’s unmatched style of mentorship:

“I chose to work with Dr. Nathan early in my first year at Pritzker because of how highly he valued medical students in research and the excellent balance he struck between autonomy and guidance for student-led projects. The first time I was introduced to the intravascular ultrasound (IVUS) technology system, he brought me into the catheterization laboratory like I had been his fellow for years. He spoke with me at a high level of complexity, challenging me to understand him while at the same time conveying a huge amount of respect to a first-year student. I was thoroughly impressed with his expertise in his field. Combined with the nature of intravascular ultrasound research requiring a quantitative, engineering background, I knew that joining Dr. Nathan’s laboratory would be one of the best decisions I could make in medical school. In relation to my growth and development, he taught me the value of broadening one’s research interests to create a diverse research profile… Through my work with Dr. Nathan, I have developed more than just a supportive research mentor. He is a true friend and colleague that I will continue to value for personal, clinical, and research support throughout my training and into my career.”
Olufunmilayo Olopade, MD

Dr. Olopade is an academic clinician known globally for her work on cancer risk assessment and individualized treatment of breast cancer. She has developed innovative strategies for the management of breast cancer based upon novel understanding of gene alterations in individual patients. In her scholarly approach, she emphasizes risk reduction strategies and prevention in high-risk populations, in addition to detection via advanced imaging technologies. She is the Walter L. Palmer Distinguished Service Professor of Medicine and Human Genetics, Associate Dean for Global Health, and Director of the Center for Clinical Cancer Genetics. In 2005, Dr. Olopade was awarded the prestigious John D. and Catherine T. MacArthur Genius Fellowship.

Dr. Olopade received the John D. Arnold, MD Mentor Award for her work with fourth year student Elizabeth “Liz” Poli. Dr. Olopade and Liz worked diligently together on projects studying the regulation of MicroRNA-29c in breast cancer, as well as the expression of the BRCA1 Pseudogene in ovarian cancer. In reflecting upon her appreciation for Dr. Olopade’s guidance as a mentor, Liz commented:

“[Dr. Olopade] pushes her students to be independent and think critically about planning successful and efficient experiments. She expects that everyone will put in their best effort to their work and strive for excellence. She also encourages a great working environment in the lab…Dr. Olopade has been a great role model for me. As a young student about to enter residency, I look up to her ability to balance being a successful female physician-scientist, having a family, being a devoted patient care-giver, teaching the several students, residents and fellows that rotate with her on service and work in her lab, and pursuing global-health projects. I am inspired by her confidence, ambition, and passion for everything she does. In addition, she is very kind-hearted and approachable.”

Russell Reid, MD, PhD

Dr. Russell Reid is highly reputed as a talented surgeon, with special expertise in pediatric plastic surgery, specifically with focus on the face, jaw, palate, and skull. As an academic clinician, Dr. Reid has disseminated widely through several book chapters and peer-reviewed journal articles published. His scholarly interests are in the areas of bone regeneration for the repair of complex craniofacial defects, the biology of skull and facial sutures, and genetic expression in craniofacial development. He serves as Associate Professor of Surgery and the Bernard Sarnat Scholar of Craniofacial Research.

Dr. Reid received the John D. Arnold, MD Mentor Award for his work with fourth year student Maureen Beederman. Together, Dr. Reid and Maureen focused tirelessly on developing new knowledge regarding the role of the RANK-RANKL-OPG pathway in suture patency and fusion. In commenting on Dr. Reid’s exemplary mentorship, Maureen commented:

“Since I began working on this project in 2010, I have found Dr. Reid to be an extremely accessible and supportive mentor, who always makes time to discuss my progress and results, offer helpful suggestions, and engage in troubleshooting with me. Working for Dr. Reid has allowed me to mature as a researcher, as he encourages critical thinking and gives me the independence to design new experiments. Dr. Reid is also an outstanding teacher, explaining challenging concepts and helping me understand the greater context behind some of our experiments and how they relate to other research in the field. Throughout my short research career, I have had the opportunity to work in a variety of different lab environments, and I have found this to be a very supportive lab environment, which has, in turn, made me a more productive and confident researcher.”
Oral Presentations
Colon Cancer Screening Behavior in a Nationally-Representative Sample of Married Couples: Do Spouses Influence Each Other?

Ashwin Kotwal, MS

*Mentor:* William Dale, MD, PhD, Department of Medicine, Section of Geriatrics and Palliative Medicine

*Co-Authors:* Diane Lauderdale, PhD; Linda Waite, PhD

**Background:** Being married is associated with higher colorectal cancer screening rates, but little is known on how each spouse influences the other's screening decisions. Using a unique national sample of older married couples with detailed information on both partners, we assessed screening colonoscopy rates of each spouse, measured whether these rates are correlated, and identified characteristics of each partner and their relationship that influenced the likelihood of screening for both.

**Methods:** We use a nationally-representative sample of 804 older male-female couples (n=1608 individuals) which is a subset of the larger National Social life Health and Aging Project (NSHAP) Wave 2 sample (n=3,137). The primary outcome is screening colonoscopy in the past 5 years. We use a bivariate probit regression model to simultaneously estimate multiple regression equations for each spouse, as a function of sociodemographic, health status, health behavior, and relationship quality covariates. We estimate the adjusted correlation of colonoscopy screening behavior within spouses and identify predictors of increased screening.

**Results:** Adjusting for covariates, the association of marital status with colonoscopy screening rates is stronger in men than in women (p-value of interaction=0.008); married men have higher colonoscopy screening rates than unmarried men (61% versus 52%, p=0.023), but there was no association for women (57% versus 60%, p=0.27). Within married couples, there is a significant correlation between colonoscopy utilization in husbands and wives after adjusting for shared characteristics (ρ = 0.26, p<0.001). Wives' characteristics are associated with husbands' likelihood of receiving a colonoscopy, but the reverse is not observed. Husbands with wives who are more highly educated are more likely to get screened (71% vs 52%, p=0.032), as are husbands whose wives are happy with the relationship (65% vs 50%, p=0.008).

**Conclusion:** In a nationally-representative sample of married couples, older husbands' and wives' screening colonoscopy rates are significantly correlated. However, marriage only increases the rates of screening colonoscopy for men, especially for men whose wives are more educated and happier with their relationship. Recognizing how marital status and quality influence colonoscopy screening rates, particularly for men, can help providers deliver more effective screening recommendations and improve adherence.

**Acknowledgements/Disclosures:** This study was supported by a Clinical and Translational Science Award (CTSA) TL1 pre-doctoral Training Grant; This work was further supported by funding for MERIT Award R37 AG030481 (PI: Waite) from the National Institute on Aging and from the National Institutes of Health for the National Health, Social Life, and Aging Project (NSHAP R01AG021487, R37AG030481) and the NSHAP Wave 2 Partner Project (R01AG033903); The University of Chicago Calvin Fentress Fellowship Recipient.
Lower Socioeconomic Status is an Independent Predictor of Major Adverse Cardiac Events (MACE) and Increased Mortality Post-Percutaneous Intervention in Public Health System Patients

Emily Guhl

Mentor: Sandeep Nathan, MD, Department of Medicine, Section of Cardiology

Co-Authors: Ali Mithani MD; Steve Attanasio DO; Andrew Appis, MD; Tamar Polonsky, MD

Background: Disparities in cardiovascular outcomes in lower socioeconomic status patients are evident, however limited data exist evaluating post-percutaneous intervention (PCI) outcomes. In the present study, we sought to assess long-term clinical outcomes post-PCI in lower vs. higher SES patients. We focused on the distribution and impact of cardiac risk factors.

Methods: 2,000 consecutive patients undergoing PCI over 6 years at Cook County Hospital, Chicago, IL were studied. Availability of complete data and planned follow-up within the PHS was mandatory for inclusion. SES was assessed via a validated proxy, geographic household income determination, and dichotomized into above/below median income for the population. All patients were followed for occurrence of MACE (death, myocardial infarction and urgent revascularization). Descriptive statistics and survival analyses using Kaplan-Meier and log-rank test were performed.

Results: 1,985 patients (age 57.2± 10.2, 31.9% female, 36.4% diabetes, computed median income $38,044) underwent PCI for STEMI (19.3%), NSTEMI (26.9%), unstable angina (24.0%), stable angina (20.3%), or LV dysfunction (3.3%). Clinical follow-up was obtained in 97.3% (mean 2.5 ± 1.9 yrs). There was significantly greater (9.2% absolute / 30% relative) MACE and mortality in lower-SES patients, with the gap steadily increasing over time (Fig 1.) In contrast to our prior study, several important risk factors were more prevalent in lower-SES patients: female gender, smoking, cerebrovascular disease, unstable presentation. The majority (71%) of lower-SES patients were black whereas the higher-SES group was more racially diverse.

Conclusion: Lower socioeconomic status portends remarkably poor post-PCI outcomes even when access to care is uniform within a PHS hospital. The impact of unevenly distributed risk factors is noted and currently being studied in a multivariate model. Racial disparities pose another concerning, if poorly understood, variable. This is the first report to our knowledge of SES-linked major adverse cardiac events in the context of a contemporary PCI experience with uniform healthcare access.

Acknowledgements/Disclosures: Sandeep Nathan, MD, is a consultant for Volcano; The University of Chicago Calvin Fentress Fellowship Recipient.
Bringing to Light Associations Between Pain, Depression and Sleep in Hospitalized Adults

Marie Adachi

Mentor: Vineet Arora, MD, MAPP, Department of Medicine, Section of General Internal Medicine

Co-Authors: Lisa Spampinato, BS; Kristen Knutson, PhD; David Meltzer, MD, PhD; Eve Van Cauter, PhD

Background: Hospitalized patients often suffer from uncontrolled pain, which could put them at risk for poor sleep in-hospital and lower energy levels the subsequent day. Furthermore, patients at risk for depression could be at even greater risk for nighttime pain, poor sleep quality and lower energy levels. We characterized the associations between depression, pain, sleep quality and morning energy levels among hospitalized seniors.

Methods: We conducted a prospective cohort study of inpatients over age 50. Exclusion criteria were cognitive impairment, preexisting sleeping disorders, isolation precautions, not ambulatory, transfer from the ICU, and institutionalization prior to admission. Patients were screened for depression on admission using the 5-item Geriatric Depression Scale (score 2 or higher indicating depressive symptoms). Nighttime pain was measured by asking patients how disrupted their sleep was from pain on a 5-point scale (1 not disrupted). Morning energy level was measured using a modified Visual Analog Mood Scale for vigor (range 0-100, higher scores indicating higher alertness). Objective sleep duration and efficiency (percent time asleep while in bed) were obtained via wrist actigraphy. For a subset of patients, light levels were measured in lux using sensors in the actigraphy watches. Associations between depression, pain, objective sleep, and energy levels were assessed using multivariable linear regression and adjusted for age, sex, race, BMI and disease severity and clustered by subject.

Results: From April 2010 to February 2014, 292 patients (mean age=65, 57% female) completed all data collection for a total of 485 nights. Average inpatient sleep duration and efficiency via actigraphy was 305min (95% CI 292, 318) and 68.6% (95% CI 66.6, 70.6), respectively. Roughly 2 of every 5 patients (124, 42%) screened positive for depression and also reported some nighttime pain (40%) disrupting their sleep. In regression analysis, reports of nighttime pain were associated with 40 fewer minutes of sleep [(95% CI -67.1, -12.8), p=.004] and 12 fewer points on the vigor score [(95% CI -17.5, -7.5), p<.001]. Furthermore, depression was associated with 48 fewer minutes of sleep [(95% CI -78.1, -17.0, p=.028], 8.3% worse sleep efficiency [(95%CI -13.3, -3.2), p=0.002], 13 fewer points on the vigor score [(95% CI -18.2, -6.5), p<.001] and increased odds of being disrupted by nighttime pain [OR=.90, (95% CI .44, 1.36), p<.001]. These relationships persisted even after controlling for demographic factors. Light levels were obtained for a subset of patients (n=111, 161 nights). Median daytime light was 19.2 lux, with only 10% of rooms meeting recommended light level for a ward room (>100 lux). Median nighttime light was 1.3 lux, with 78% of rooms meeting recommended night lighting for a ward room (<5 lux).

Conclusion: Many hospitalized patients are depressed and report nighttime pain disrupting their sleep. Reports of nighttime pain and positive depression screen were both associated with significantly shorter sleep duration and decreased morning energy level. Better nighttime pain control and fewer nighttime disruptions may improve sleep quality and morning alertness among adult inpatients, especially those at risk for depression. Moreover, inpatient rooms are poorly lit, failing to meet recommended light guidelines.

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The Glyoxalase System Regulates GABA-A Receptors and Anxiety

Margaret Distler, PhD

Mentor: Abraham Palmer, PhD, Department of Human Genetics

Co-Authors: Leigh Plant, PhD; Greta Sokoloff, PhD; Ivy Aneas, PhD

Background: Anxiety disorders are among the most common psychiatric disorders in the United States. Current anxiolytic drugs are not effective in all patients and can have adverse side effects. Therefore, it is important to identify novel genes and biological pathways underlying anxiety disorders in order to elucidate their pathogenic mechanisms and identify therapeutic targets. The present work investigated the role of glyoxalase 1 (GLO1) in anxiety. Previous mouse genetic studies have identified a positive correlation between Glo1 expression and anxiety-like behavior. Nevertheless, the mechanism underlying GLO1’s anxiogenic effect remains unknown. GLO1 is an enzyme in the glyoxalase system, a metabolic pathway that detoxifies methylglyoxal (MG), which is a cytotoxic byproduct of glycolysis. When MG accumulates to high levels, it induces protein modification and apoptosis. The present work investigated GLO1's effect on anxiety as well as the underlying molecular mechanism. Specifically, we hypothesized that GLO1 regulates anxiety by regulating MG concentration.

Methods: We generated transgenic mice harboring a bacterial artificial chromosome (BAC) containing Glo1 in order to model Glo1 overexpression. To establish a causal role for GLO1 in anxiety-like behavior, we tested these mice for anxiety-like behavior in the open field (OF), light-dark (LD) box, and the elevated plus maze (EPM) tests. We then tested the hypothesis that GLO1 regulates anxiety by regulating MG levels. Specifically, we administered exogenous MG to mice and assessed their anxiety-like behavior in the OF, LD box, and EPM tests. We further investigated the cellular effects of MG by using whole-cell patch clamp in cultured neurons to identify its electrophysiological effects. Finally, to confirm the therapeutic relevance of GLO1’s effect on anxiety, we treated mice with a small-molecule inhibitor of GLO1 and measured anxiety-like behavior.

Results: BAC transgenic mice overexpressed Glo1 and displayed increased anxiety-like behavior in the OF, LD box, and EPM tests. Furthermore, Glo1 overexpression caused a reduction in MG concentration in the brain, and treatment with exogenous MG decreased anxiety-like behavior in mice. At higher doses, exogenous MG administration caused sedation, decreased locomotion, and ataxia. Because this pharmacodynamic profile was consistent with activation of γ-aminobutyric acid subtype A (GABA-A) receptors, we tested MG’s electrophysiological effects on neurons in culture. Using whole-cell patch clamp, we demonstrated that MG activated GABA-A receptors. Finally, using a small-molecule inhibitor of Glo1, we demonstrated that Glo1 inhibition reduced anxiety-like behavior in mice.

Conclusion: The present work established a causal role for Glo1 overexpression in increased anxiety-like behavior. Furthermore, we established the underlying molecular mechanism. Glo1 overexpression reduced levels of MG; MG was anxiolytic in vivo and activated GABA-A receptors in vitro. GABA-A receptors have a well-established role in the pathogenesis of anxiety disorders. Therefore, we concluded that Glo1 increases anxiety by clearing MG, an endogenous anxiolytic agent that activates GABA-A receptors. These findings have important implications for central nervous system physiology, providing a potential mechanism whereby metabolic state regulates neuronal inhibitory tone and behavior. Finally, because Glo1 inhibition reduced anxiety-like behavior in mice, Glo1 may be a novel target for the treatment of anxiety.

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Prolactin Receptor-Mediated Internalization of Imaging Agents Detects Epithelial Ovarian Cancer with Enhanced Sensitivity and Specificity

Karthik Sundaram, PhD

**Mentor:** Joseph Piccirilli, PhD, Departments of Biochemistry and Molecular Biology & Chemistry

**Co-Authors:** Ernst Lengyel, MD, PhD; Anthony A. Kossiakoff, PhD; Brian R. Roman, PhD

**Background:** The poor prognosis of ovarian cancer (OvCa), the deadliest of the gynecologic malignancies, reflects major limitations associated with detection and diagnosis. Current methods lack sensitivity to detect small tumors, precluding diagnosis of early and metastatic cancer stages, and lack specificity to distinguish malignant from benign tissue, leading to costly and invasive surgeries. Targeted imaging offers significant potential to improve selectivity and diagnosis, however due to lack of viable molecular targets, few such opportunities have emerged for OvCa. Seeking to overcome these limitations, we hypothesized that the prolactin receptor (PRLR), an upregulated receptor tyrosine kinase in OvCa that mediates ligand-induced endocytosis, could serve as a vehicle for specific delivery of imaging agents to OvCa.

**Methods:** We used tissue microarray analysis to identify the prolactin receptor (PRLR) as a high specificity biomarker for malignant OvCa. We fused human placental lactogen (hPL), a specific and tight binding PRLR ligand, to magnetic resonance imaging (gadolinium) and near-infrared fluorescence imaging agents. We then evaluated internalization by PRLR (+) and PRLR (-) ovarian cancer cells. We further evaluated that capacity of hPL-conjugates to imaging mouse xenografts of human ovarian cancer by magnetic resonance imaging and near-infrared fluorescence imaging.

**Results:** Our results indicated that relative to normal ovarian tissue, >98% of OvCa express moderate to high levels of PRLR, regardless of stage, grade or histology, establishing PRLR as a robust biomarker for many OvCas. Using our hPL-conjugates, we showed by immunoblotting, confocal microscopy, and ICP-MS that these imaging conjugates bind to PRLR+ tissues and selectively internalize into PRLR+ cells in a zinc, PRLR, and hPL dependent manner, demonstrating a mechanism of uptake involving PRLR-mediated endocytosis. When these NIRF and MR imaging conjugates were administered to athymic nude mice bearing subcutaneous serous-papillary tumors, fluorescence molecular tomography and MRI, respectively, revealed that these agents selectively localized to the PRLR over-expressing OvCa tumors, enabling highly sensitive and specific detection of these tumors. Ex vivo imaging and ICP-MS analysis of organs confirmed the selective localization. Additionally, we could detect tumors as small as 10 mg, including small, disseminated peritoneal tumors that mimic metastatic OvCa. Compared to Magnevist, a contrast agent used currently in clinical MRI, our hPL-conjugate achieved a 100-fold improvement in threshold of detection.

**Conclusion:** Collectively, our data establish PRLR as a robust biomarker for many OvCas. The receptor’s capacity to mediate internalization of hPL imaging conjugates via receptor-mediated endocytosis allows detection of small ovarian tumors with enhanced signal to noise ratio and improved specificity conferred by OvCa-specific PRLR expression. Together these findings form the conceptual underpinnings of a new paradigm for imaging OvCa with potential to enable early diagnosis, eliminate unnecessary surgeries, and improve postoperative disease management.

**Acknowledgements/Disclosures:** None.
Alpha-Defensin 5 Expression is Regulated by microRNAs in Colonic Epithelial Caco-2 Cells

Donald (Bailey) Miles

Mentor: John Kwon, MD, PhD, Department of Medicine, Section of Gastroenterology

Co-Authors: Jun Shen, MD; Alice Y. Chuang, MD; Feng Wu, MD, PhD

Background: In inflammatory bowel disease (IBD), there is an inappropriate immune response that leads to chronic mucosal inflammation. This immune response may be in part due to dysregulation of the innate immune system, including defensins, a class of antimicrobial peptide. The alpha-subtype of defensins is produced by Paneth cells in the small intestine in response to bacterial endotoxins and cytokines and acts as a first-line defense against microbes. A decrease in alpha-defensins could contribute to IBD pathogenesis by allowing bacterial overgrowth, epithelial adherence, and bacterial invasion with inflammation. Despite the important role of defensins in the pathogenesis of IBD, the regulation of alpha-defensins is unknown. This study was designed to determine whether microRNAs (miRNAs) regulate alpha-defensin 5 (HD5) expression in colonic epithelial Caco-2 cells.

Methods: Induction of HD5 mRNA and protein expression by FGF-2 alone and with TNFalpha was determined in post-confluent Caco-2 cells. HD5 mRNA expression was measured by quantitative reverse transcription-polymerase chain reaction (qRT-PCR). HD5 protein expression was measured by Western blot following protein separation by tricine-SDS-PAGE. An in silico analysis was conducted using miRBase and TargetScan to identify putative miRNA binding sites in the 3’ UTR of DEFA5, the gene encoding HD5. Expression of these putative regulatory miRNAs was assessed by qRT-PCR in induced Caco-2 cells. Regulation of HD5 expression by these miRNAs was assessed by luciferase reporter construct assays. MiRNA regulation of HD5 was confirmed by measurement of HD5 mRNA and protein expression after transfection of Caco-2 cells with miR-124 and miR-924 mimics.

Results: Caco-2 cells stimulated with FGF-2 alone and FGF-2 in combination with TNFalpha resulted in a statistically significant increase in HD5 mRNA and protein expression. Fifteen putative miRNA binding sites were found in the 3’ UTR of the DEFA5 gene. The expression of the two most highly expressed miRNAs with binding sites in the DEFA5 3’ UTR, miR-124 and miR-924, decreased following induction with FGF-2 alone and in combination with TNFalpha. This expression pattern was inversely correlated with HD5 mRNA expression. Transfection of a pmirGLO reporter construct containing the DEFA5 3’ UTR resulted in a statistically significant decrease in relative luciferase activity compared to transfection of the empty vector. A pmirGLO reporter construct containing the DEFA5 3’ UTR with mismatched binding sites of either miR-124 and miR-924 was transfected into Caco-2 cells, resulting in a statistically significant restoration of relative luciferase activities, indicating that mutation of the miRNA binding site led to a loss of regulation by that particular miRNA. Finally, transfection of the miR-124 and miR-924 mimics significantly decreased both HD5 mRNA expression and protein expression.

Conclusion: To our knowledge, this is the first report demonstrating that miRNAs regulate HD5. Two miRNAs, miR-124 and miR-924, negatively regulate the expression of HD5 mRNA and protein. These data further implicate miRNA regulation in the pathogenesis of IBD. This study also confirms the role of miR-124 in IBD and establishes a novel role for miR-924 in IBD. Further understanding of miRNA regulation in IBD may lead to potential diagnostic and therapeutic strategies in IBD patients.

Acknowledgements/Disclosures: NIH T32 DK007074 (PI: Eugene Chang); The University of Chicago Calvin Fentress Fellowship Recipient.
An NF-kB Dependent Gene Set Identifies the Long Non-Coding RNA, MALAT1, as a Novel Target for Use in Malignant Glioma

David Voce

Mentor: Bakhtiar Yamini, MD, Department of Surgery, Section of Neurosurgery

Co-Authors: Clayton Crawley, PhD; Giovanna Bernal, PhD; Kirk Cahill, MS3

Background: Despite aggressive treatment, median survival for patients with malignant glioma (GBM) remains less than 12 months. The addition of temozolomide (TMZ), an orally bioavailable alkylating agent, has extended survival by 2 months, resulting in TMZ becoming the standard therapeutic agent. However, resistance quickly reduces TMZ’s effectiveness.

Previous work in our laboratory determined that nuclear factor-kB (NF-kB) is necessary for efficient induction of apoptosis from alkylating agents. Specifically, our studies indicated that loss of the p50 (NF-kB1) subunit attenuates TMZ cytotoxicity. As NF-kB is a transcription factor, we hypothesized that depletion of NF-kB diminishes TMZ killing by altering the basal and TMZ-induced cellular gene expression profile. Identification of these altered genes could provide potential targets to improve TMZ efficacy.

Methods: Intracranial xenografts of stable p50 and control shRNA-expressing U87 glioma clones were established in mice to test the p50-dependency of TMZ. An Affymetrix U133 Plus 2.0 Gene Chip was used to detect changes in the p50-dependent expression profile. Data was analyzed in the Bioconductor Suite and interrogated against five glioma databases. EMSA, ChIP, and luciferase studies were employed to study MALAT1 regulation. Nanoparticles with siRNA directed against MALAT1 were given using convection enhanced delivery (CED) to mice with glioma xenografts.

Results: Mice with intracranial glioma xenografts with deficient p50 expression have a diminished response to TMZ therapy, supporting p50’s critical role in the TMZ induced killing response. To identify potentially important genes, we analyzed the gene expression profile induced by TMZ in p50-proficient and deficient cells. A p50-dependent 10-gene set was identified with the predictive power to separate glioma patients by prognosis. Within this gene set, the lncRNA, MALAT1, was identified and shown to hold independent predictive value – patients whose tumors have high expression of MALAT1 have significantly worse prognosis, suggesting high expression of MALAT1 is related to survival of cells and patient death. Using TMZ in combination with nanoparticles with a payload of siRNA targeting MALAT1 significantly improves survival of mice with glioma xenografts. While this data indicates MALAT1 is regulated in a p50-dependent manner, data from a genome wide analysis of damage-induced intergenic DNA suggests the potential for regulation in a p53-dependent manner. Examination of the MALAT1 promoter region reveals a putative p53 binding site and two NF-kB binding sites. Taken together, data from ChIP, EMSA, and luciferase reporter studies indicate induction of MALAT1 occurs in a p50 and p53 co-dependent, reciprocal manner. Specifically, TMZ reduces p50 binding and increases p53 binding to respective promoter sites. Interestingly, in cells with deficient levels of p50, TMZ is unable to induce an increase in p53 promoter binding, indicating a codependence of p53 and p50.

Conclusion: Our data demonstrates p50 is critical to the TMZ-induced anti-glioma effect and identifies a 10-gene p50-dependent gene set that separates patients according to prognosis. One of these genes, MALAT1, independently stratifies patients. MALAT1 expression is induced by TMZ treatment, a process that is co-regulated by p50 and p53. We show that blocking MALAT1 expression improves TMZ efficacy and leads to improved survival.

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Becoming a Better Intern:  
The Fundamentals of Radiology in Internal Medicine

Adam Schwertner

Mentor: Christopher Straus, MD, Department of Radiology

Background: Radiology has become a vital part of patient care in internal medicine and most other specialties. Medical students across the nation have varied experiences in clinical radiology during medical education and there are many radiologic concepts that need to be understood for an intern to succeed during the first year of residency. There is a void of easily accessible and interactive radiology learning content that exists for graduating medical students. A thorough and peer-reviewed radiology learning module intended for graduating senior medical student would be a beneficial resource.

Methods: Content for an internal medicine based learning module was generated by meeting with internal medicine residency program directors to discuss what content would make an intern successful. Once content was established, a learning module was created from references in radiology textbooks. A pre-module and post-module survey was created and administered to 4th year medical students at the University of Chicago who had gone through the module. The surveys assessed student preparedness to interpret radiologic images, understand vocabulary in radiologic reports, order the correct imaging study, and work with radiologists in patient care.

Results: Pre-module surveys were completed by 21 medical students and post-module survey were completed by 16 medical students. Using a Likert scale from 1 to 4 where 1 is very unprepared, 2 is unprepared, 3 is prepared, and 4 is very prepared; students’ average preparedness to interpret radiologic images on the pre-survey was 2.38 compared to 3.06 on the post-survey (p-value, 0.002). Students’ average preparedness to order the correct imaging study based test in various clinical scenarios was 2.24 on the pre-test and 3.19 on the post survey (p-value, 0.00007). Students’ average preparedness to understand vocabulary used in radiology reports was 2.66 on the pre-survey versus 3.56 on the post survey (p-value, 0.00007). Students’ average confidence working with radiologists in patient care was a 2.53 on the pre-survey and 3.56 on the post-survey (p-value, 0.00001). The average time taken to complete the module was 86.5 minutes with a standard deviation of 44.8 minutes and 100% of the students felt that the module covered enough material. 56% of students felt the module would be most helpful to go through during the third year of medical school

Conclusion: Students felt significantly more prepared to perform radiology related tasks after completing this learning module covering the fundamentals of radiology in internal medicine. More than half of the students even thought the module would be beneficial to complete during the third year of medical school to help succeed during clerkships.

Acknowledgements/Disclosures: None.
QTc Prolongation at an Academic Medical Center: Quantifying the Risk from Medications

Fady Riad

Mentor: Andrew M. Davis, MD, MPH, Department of Medicine, Section of General Internal Medicine

Co-Authors: Michael P. Moranville, PharmD; Joshua D. Moss, MD, FHRS; Hemal M. Nayak, MD, FHRS; John F. Beshai, MD, FHRS

Background: QTc prolongation has a prevalence of 30-60% and is associated with increased all-cause mortality. QTc prolonging medications are often used despite QTc changes during hospital stay, highlighting the need for greater attention to this issue. The Arizona Center for Education and Research on Therapeutics (CERT) keeps an updated list of medications causing QTc prolongation; however, few quantitative data have been reported regarding the real world relative risk of QTc prolongation in the hospital setting.

Methods: We used electronic medical records to identify patients ≥18 years old receiving an EKG at the University of Chicago Medicine, admitted in 2011. The longest QTc interval and medications administered within the preceding 24 hours were evaluated. Prolonged QTc was defined as >450 msec in men and >460 msec in women.

Results: A total of 14,804 patients met the study criteria. Mean QTc intervals were 31ms longer for men and 16ms longer for women receiving known risk medications compared to those not receiving any conditional, possible, or known risk medications (p<0.0001). The rate of QTc prolongation was 71% vs 48% for men and 50% vs 34% for women respectively. We did not observe a significant increase in QTc prolongation for patients administered multiple QT-relevant medications or for those administered only conditional or possible risk medications.

Conclusion: There is substantial prevalence and inadequate awareness of significant QTc prolongation among patients receiving Arizona CERT known risk medications. Policies should be implemented to monitor and respond to QTc changes in these patients.

Acknowledgements/Disclosures: None.
Medical Students as Hospice Volunteers: Reflections on an Early Experiential Training Program in End-of-Life Care Education

Melissa Mott, PhD

Mentor: Stacie Levine, MD, Department of Medicine, Section of Geriatrics and Palliative Medicine

Co-Authors: Rita Gorawara-Bhat, PhD

Background: Despite an increase in the content of palliative medicine curricula in medical schools, students are rarely exposed to end-of-life (EOL) care through real-patient experiences during their pre-clinical education.

Methods: Patients and Families First (PFF), a hospice volunteer training program in EOL care, was piloted on three cohorts of MS-1s as an elective. Fifty-five students received 3 hours of volunteer training, and were then required to conduct at least two consecutive hospice visits on assigned patients to obtain course credit. Students’ reflective essays on their experiences were analyzed using qualitative methodology and salient themes were extracted by two investigators independently and then collaboratively.

Results: The following five themes were identified from students’ reflective essays: 1) Perceptions regarding hospice patients 2) Reactions regarding self 3) Normalcy of EOL care at home 4) Impact of witnessing death and dying 5) Suggestions for improving EOL care for medical students

Conclusion: Hospice volunteering during pre-clinical years may provide valuable experiential training for MS-1s in caring for seriously ill patients and their families by fostering personal reflection and empathic skills, thereby providing a foundation for future patient encounters during clinical training.

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Applied Scholarship
IBCD: Development and Testing of a Checklist to Improve Quality of Care for Hospitalized General Medical Patients

Anthony Aspesi

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**Background:** Several studies have demonstrated the usefulness of medical checklists to improve quality of care in surgery and the ICU. The feasibility, effectiveness, and sustainability of a checklist was explored.

**Methods:** Literature on checklists and adherence to quality indicators in general medicine was reviewed to develop evidence-based measures for the IBCD checklist: (I) pneumococcal immunization, (B) pressure ulcers (bedsores), (C) catheter-associated urinary tract infections (CAUTIs), and (D) deep venous thrombosis (DVT) were considered conditions highly relevant to the quality of care in general medicine inpatients. The checklist was used by attending physicians during rounds to remind residents to perform four actions related to these measures. Charts were audited to document actions prompted by the checklist.

**Results:** The IBCD checklist was associated with significantly increased documentation of and adherence to care processes associated with these four quality indicators. Seventy percent (46/66) of general medicine teams during the intervention period of July 2010-March 2011 voluntarily used the IBCD checklist for 1,168 (54%) of 2,161 patients. During the intervention period, average adherence for all four checklist items increased from 68% on admission to 82% after checklist use (p < .001). Average adherence after checklist use was also higher when compared to a historical control group from one year before implementation (82% versus 50%, p < .0001). In the six weeks after the checklist was transitioned to the electronic medical record, IBCD was noted in documentation of 133 (59%) of 226 patients admitted to general medicine.

**Conclusion:** A checklist is a useful and sustainable tool to improve adherence to, and documentation of, care processes specific to quality indicators in general medicine.

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Advance Care Planning Interviews with Geriatric Trained Patients During Home Visits

Carly Berg

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Background: Since 2010, the LCME has required end-of-life care training in medical schools. The teaching of communication skills is an important component of this training. The use of role plays and standardized patient scenarios to teach communication skills have been published in the literature, but the use of patients trained as educators (“trained patients”) in non-standard scenarios has not been fully characterized.

The positive experience at Pritzker with the Geriatrics and Aging through Transitional Environments (GATE) curriculum, which utilized home visits with trained patient volunteers to teach functional history-taking communication skills, provided an opportunity for further development and evaluation of curricula utilizing trained patients. A curriculum on Advance Care Planning (ACP) discussions using trained patients was developed to be integrated into the MS-3 Family Medicine clerkship.

Methods: The new curriculum was developed around a semi-structured ACP interview conducted by medical student(s) with a geriatric trained patient in the trained patient's home. Prior to the interview students completed an online module on ACP and were provided with supplementary reading materials and a video demonstration of the interview. The trained patients were recruited from Montgomery Place Retirement Community in Hyde Park. They completed a bi-annual training session that addressed the goals, objectives, and structure of the interview as well as the fundamentals of verbal feedback.

Following the interview, students completed a retro-pre/post survey addressing their confidence levels in skills related to ACP discussions and their evaluation of the components of the curriculum, and they wrote a 250-word reflective essay on their interview experience. The trained patients submitted written evaluations of the students’ communication skills from the patient perspective.

Results: The first year of the program was completed in the 2012-2013 academic year. 83 third-year medical students and 22 trained patient volunteers participated.

Curriculum evaluation included analysis of the reflective essays using grounded theory qualitative analysis and analysis of the survey results using paired t-tests when appropriate. Five major themes were identified in the reflective essays: 1) Students’ initial apprehension or discomfort with the task; 2) Importance of understanding and respecting patients’ end-of-life preferences; 3) Recognizing patients’ values and definitions of quality of life; 4) Importance of timing ACP when patients are healthy and re-visiting the topic regularly; 5) Value of practicing ACP discussions with actual patients.

Survey analysis showed that students rated their confidence in skills related to ACP discussions significantly higher (p < 0.001) across all seven domains following the completion of the curriculum.

Conclusion: Practice interviews on advance care planning with trained patients improve students’ confidence in discussing ACP with patients. The experience of practicing ACP discussions with trained patients enabled students to recognize the importance of these conversations and of understanding patients’ values, beliefs and preferences.

Acknowledgements/Disclosures: None.
Labor and Delivery Handoff Curriculum Development

Saba Berhie

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**Background:** Patient handoffs are a fraught transition. Trainees have limited formal teaching and awareness of the importance of the handoff for patient safety and quality of care. There is little handoff specific literature in Obstetrics and Gynecology and the PM handoff to the night float team transitions patients to a new set of residents who are dependent on the handoff to provide quality care.

**Methods:** Building on previous work characterizing interruptions during the University of Chicago Labor and Delivery AM and PM sign-out we created a didactic intervention for the Ob/Gyn residents. A script for a 4-minute video was written. It included common medical scenarios on labor and delivery and was evaluated by our Ob/Gyn collaborator for accuracy of language and pacing. The script incorporated issues from previous work on Labor and Delivery handoffs and contained the most common interruptions, patient safety issues, questions of role definition, and errors. A video was then filmed using actors. A handoff didactic day was scheduled for the Ob/Gyn residents and the video was shown with a presentation of handoff patient safety and quality data. After the video was shown a discussion of possible handoff solutions was had with the residents. Notes were taken during the discussion and disseminated to the residents.

**Results:** On May 2nd, 2014 eight residents participated in the handoff didactic day. Three fourth year residents, one third year, two second years, and two interns were present. The ideas that came out in conversation included: structural changes to reduce interruptions, role definitions before sign-out, and communication strategies to standardize the handoff.

**Conclusion:** This educational intervention was feasible and the residents who participated were very interested in having a conversation after watching a video that demonstrated handoff issues collected from observations of University of Chicago handoffs. They were very invested in the idea of improving the handoff and saw it as an important part of the patient care they provide.

The next step is to observe handoffs at both the University of Chicago Medicine and NorthShore University HealthSystem to see if the didactic day permeated the culture and changes the handoff quality by tabulating the rates of interruptions, side conversations, and role definition issues compared to previous work done observing handoffs in January-March 2013.

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Medical Students’ Intentions to Practice Among the Underserved: A National Survey of 3rd and 4th Year Students

Theodore Hart

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Background: The scarcity of physicians practicing among underserved populations highlights a national concern regarding physician workforce shortages. The discussion for potential solutions is often directed to U.S. medical schools, which are responsible for the matriculation and education of students that will eventually care for the national population. Previous studies have demonstrated that underrepresented minority students and those who grew up in medically underserved communities are more likely to practice in underserved areas. Some medical schools have also developed interventions that successfully increased practice with underserved populations. However, no studies exist on a national level that examine characteristics of students who intend to practice among the underserved in the context of the varying educational experiences students obtain in medical school. This study examines self-reported characteristics of students intending to practice among the underserved during the clinical years of medical school.

Methods: A survey was administered by mail to a nationally representative random sample of 960 allopathic medical students during their third year clerkships, with a follow up survey performed during their fourth year.

Results: The response rate was 46%. Thirty-four percent of fourth year students reported an intention to locate their practice in a medically underserved area—an overall increase from 30% as third year students. Fourth year students more likely to report an intention to practice among the underserved included underrepresented minorities (multivariate odds ratio [OR] 3.1; 95% confidence interval [CI] 1.5-6.7), those who grew up in a medically underserved community (OR 3.4; 95% CI 2.0-5.7), students with a high sense of calling (OR 3.8; 95% CI 2.0-7.2), students who self-identified as highly spiritual (OR 2.5; 95% CI 1.3-4.7), and students with a high sense of vocational identity (OR 1.9; 95% CI 1.2-3.0). Men were less likely to indicate a preference for underserved practice (OR 0.4; 95% CI 0.2-0.6); this was also observed students who were elected as members of Alpha Omega Alpha (OR 0.4; 95% CI 0.2-0.9). Students were also stratified based on their school’s Social Mission Score, a ranking system published by Mullan and colleagues in 2008 that accounts for a medical school’s percentage of minority graduates, percentage of graduates practicing in healthcare provider shortage areas, and percentage of graduates practicing primary care. Students from low-ranking schools were less likely than peers at high-ranking schools to indicate an intention to practice among the underserved. Rankings 1-30 (referent), ranking 31-64 (no statistically significant difference), rankings 65-110 (OR 0.5; 95% CI 0.3-0.9), rankings 111-140 (OR 0.4; 95% CI 0.2-0.8).

Conclusion: In addition to demographic factors and experiences prior to medical school, students’ intentions to practice among the underserved are predicted by their sense of calling and vocational identity, as well as by their spirituality and the social mission of their medical school. The interactions between these factors are complex, but this study provides important considerations at both an individual and institutional level for medical educators and policy makers working to increase practice among the underserved.

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Accreditation and Subspecialization in Neurology Fellowships

Trent Hodgson

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Background: Clinical practice in neurology has actively diversified in the past 20 years, and there has been an increase in the number and types of fellowship programs to accommodate these changes. In order to facilitate expansion and guide subspecialization, accrediting bodies began in the 1990s to accredit fellowship programs and to administer certification exams to qualified physicians. This study considers the effect of these policies by studying the closely related fields of vascular neurology, which was first certified in 2005 by the American Board of Psychiatry and Neurology (ABPN), and neurocritical care, which was first certified in 2007 by the United Council of Neurologic Subspecialties (UCNS).

Methods: We cross reference publicly available lists of diplomates and compile historical information on the growth rates of fellowship programs and which of their graduates held multiple degrees.

Results: Vascular Neurology and Neurocritical Care are rapidly expanding. However, the initially high percentage of individuals with both certifications (65.9%) has decreased significantly over time (18.9% in 2013, p<0.01). This likely reflects a divergence of these fields, which would represent increased subspecialization since certifications were first issued in 2007. In addition, for individuals with both certifications, there is a significant trend towards earning a UCNS neurocritical care certification after the ABPN vascular neurology certification, which could indicate the increasing stature of the recently founded UCNS.

Conclusion: The availability of optional accreditations for fellowship programs and certification exams for qualified subspecialists has the net effect of increasing subspecialization. By drawing strict lines between existing specialties that overlap—and making the cost of crossing this artificial boundary prohibitively high (completing a second fellowship)—many individuals will choose to practice and research within only one subspecialty “silo” regardless of qualifications or interest. This ongoing process is most pronounced among younger neurologists and therefore its true impact may not be felt for several decades. The overall impact on the neurology labor supply, as well as regional variation, must be closely monitored as the US population grows and ages.

Acknowledgements/Disclosures: None.
GOT MeDS? Designing and Implementing an Interactive Module for Trainees on Reducing Drug Costs

Rupali Kumar

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Co-Authors: Neel Shah, MD, MPP; Andrew Levy, MD; Mark Saathoff; Jeanne Farnan, MD, MHPE

Background: Patients are facing a rise in the out-of-pocket cost of drugs. Multiple studies show physicians are unaware of how much prescription drugs cost to patients. Patients and physicians agree that more discussion of patients’ out-of-pocket drug costs is necessary. While patients have expressed a desire to have their physicians educate them on the cost and quality of their treatment options, physicians are unlikely to do so. One reason is because of the lack of standard education on drug cost reduction strategies that exists in medical training. Our aim was to create an interactive educational module that makes strategies and resources for lowering patients’ prescription drug costs readily accessible and easily applicable for medical trainees.

Methods: The module was piloted with the Pritzker School of Medicine Quality and Safety Track (QST), consisting of four medical students and two attendings. Feedback on potential improvements to the module was elicited from the stakeholders and pilot participants and was subsequently incorporated into the module. Based on expert opinion from a pharmacoepidemiologist and pharmacist, literature review, and input from trainees, an educational module was designed, comprised of a PowerPoint presentation, Pocket Reference Cards, and a Video Vignette. This module was delivered to MS1s as a part of their Clinical Skills course. The participants completed pre- and post-tests to evaluate their preparedness and confidence regarding drug cost reduction strategies and counseling. Participants ranked each item 1-5 (Strongly Disagree-Strongly Agree). Paired t-tests comparing mean response on Pre- and Post-Test were performed for each item, as well as Wilcoxon signed-rank tests.

Results: The resulting curriculum used the mnemonic “GOTMeDS?” which encompassed the strategies trainees should use to reduce patient out of pocket costs: (G) Generics; (O) Ordering in bulk; (T) Therapeutic alternatives; (Me) Medication review; (D)discount programs; (S) Splitting pills. The interactive module includes a case that highlights the costs for a patient on multiple medications (ASA, statin, beta blocker, ARB, Plavix, and non-generic antidepressant) and asks trainees to use the GOTMeDS strategy along with online resources (LowestMed App & Consumer Reports Best Buy Drugs) to potentially save the patient over 50% of the cost. Paired t-tests revealed a significant increase in mean score for the following three Pre-/Post-test items: (1) “I know where to look to find the most cost-effective drugs in a particular drug class,” (2.00 vs. 3.50, p<0.01) (2) “I know where to look online for medication cost-saving resources,” (2.33 vs. 3.83, p<0.01) and (3) “I know which mobile applications are useful for medication cost-saving resources” (2.17 vs. 3.83, p<0.05). The module was implemented with all 88 first year medical students. 100% reported confidence in screening patients for difficulty to pay for medications after the session. 100% found it useful & 98% helpful for free clinics they work in. Comments were very positive: “These [are] skills easily implemented to make a very significant impact. A.k.a. SUPER high yield!”

Conclusion: An interactive educational module may improve medical trainee knowledge and confidence regarding ability to communicate with patients about drug costs. Future work will test the module on a larger scale and assess changes in practice using a standardized patient exercise to evaluate trainees behaviors in practice.

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Utility of Head CT in the Evaluation of Acute Vertigo/Dizziness in the Emergency Department

Courtney Lawhn Heath

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Background: Acute dizziness (including vertigo) is a common reason to visit the emergency room, and imaging with head CT is often performed initially to exclude a central cause. However, according to the American College of Radiologists Appropriateness Criteria, MRI may be a more useful modality for this indication. In this study, consecutive patients presenting with dizziness and undergoing head CT were retrospectively reviewed to determine diagnostic yield. In addition, physicians were surveyed to determine the most important factors that lead them to order imaging for vertigo/dizziness, as well as barriers to expanded use of MRI.

Methods: 448 consecutive head CT’s in a representative sample of dizzy ER patients, including patients with other neurological symptoms, were reviewed to identify an acute or subacute cause for acute dizziness along with the frequency and modalities used in follow up imaging. Surveys were e-mailed to a selection of 24 emergency medicine attending physicians in both community and academic settings.

Results: The diagnostic yield for head CT ordered in the ER for acute dizziness is low (2.2%; 1.6% for emergent findings), but MRI changes the diagnosis up to 16% of the time, acutely in 8% of cases. Overall, the survey revealed that emergency physicians relied heavily on head CT in clinical scenarios in which the American College of Radiology indicates MRI as being more appropriate. 92.3% cited liability concerns as the most important reason imaging may be overused in the ED. Availability of MRI at a given time was the most commonly cited challenge to expanded use of MRI (100%); length of time to obtain an MRI vs. CT was second (61.5%); other factors included patient preference/claustrophobia and difficulty of interpretation.

Conclusion: Consistent with the ACR appropriateness criteria and the literature, this study suggests a low diagnostic yield for CT in the evaluation of acute dizziness but an important role for MRI in appropriately selected cases.

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Video Based Tutorials and Guided Lab Instruction for Medical Neurobiology Course

Nicholas Ludmer

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Background: In the fall of 2011, a new curriculum for the Pritzker School of Medicine’s Medical Neurobiology Course was introduced. The course includes a laboratory component composed of nine laboratory sessions, during which students perform basic dissection, identify anatomical structures, and complete exercises designed to highlight and coincide with the functional knowledge they acquire in lecture. Instruction for these sessions, however, has presented a unique problem. Mass lecture created a difficult environment with which to demonstrate dissection and identify structures on a single brain sample, and small group instruction requires a large amount of time and personnel to be done effectively.

Methods: The goal of this project is to design, create, and evaluate multimedia resources that help to alleviate the logistical difficulties present with mass lecture as well as the resource strain inherent in small group instruction. This will be accomplished primarily through the development of a series of video tutorials/modules that will be made available to the students through the course website. The videos will contain visual demonstrations of dissection techniques, still shots and video footage of neuroanatomical samples with graphical overlays highlighting desired structures, as well as animations helping to explain their development and function. Material from the videos will coincide directly with the written exercises students are expected to complete during each of the nine laboratory sessions, as well as reference material presented in the lecture component of the course. Once available on the course website, students may review these materials both in preparation for and during lab sessions. It will also allow them to be accessed by students at all times, making them another resource students may use for review.

Results: Once incorporated into the course curriculum, the utility and efficacy of the materials will then be evaluated through student feedback and surveys administered during normal course evaluation. Upon the completion of each laboratory session, students will be sent a brief survey regarding their use and opinions regarding the video tutorials. They will also be given a survey that is included with the standardized course feedback administered through the Pritzker School of Medicine. Information from the post-lab surveys as well as the course feedback will be used to improve the presentation and content of the materials.

As not all of the videos are complete, the aforementioned assessment has not been applied. Informal surveys asking students whether or not they found the existing videos showed a positive response, with 84% of responses being “Agree” or “Strongly agree”. We expect that formal survey on completion of the video series will be positive.

Conclusion: The addition of multimedia resources will be a valuable asset for the Pritzker Medical Neurobiology course, and offer students an additional means for comprehending the material. Feedback from students will be used to guide the further development of these multimedia tools. Raw footage and software required will be saved for future use and improvement of existing videos.

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"Dear Diary": A Study Exploring Factors Impacting the Engagement of Matriculating Medical Students in Reflective Writing

Camille Petri

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Background: The ability to reflect is essential to self-evaluation and ongoing professional growth. In addition to providing a basis for self-assessment, reflection promotes effective communication skills, and can play an important role in the professional development of medical students and physicians. While there are multiple modalities employed for this reflective process, reflective writing is a practice commonly encountered in academic settings. There is growing recognition that the development of the physician begins at matriculation to medical school and is marked symbolically with the ceremonial investiture of the student with their first white coat. Because reflection has a tremendous impact on medical professionals, reflective ability is a desirable characteristic in entering medical students.

Methods: In August 2012, first year medical students at the University of Chicago were surveyed regarding reflective ability and frequency of reflective writing. The survey contained the previously validated Groningen Reflective Ability Scale (GRAS) and questions regarding frequency of reflective writing, demographics, pre-matriculation educational history, and anticipated specialty choice. The goals of the survey were to determine if scores on a self-administered rating scale were associated with frequency of reflective writing in first year medical students and to determine if there were demographic factors associated with frequency of reflective writing. All questions were measured using a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree). Factors associated with reflective writing frequency were measured using ordered logistic regression models and ANOVA tests.

Results: Fifty out of eighty-eight students (56.8% response rate) completed the survey. Students who entered medical school one or more years after graduating from college had odds of utilizing reflective writing daily or weekly that were 5.34 times the odds for a student who entered medical school immediately after college (p-value = 0.004). Majoring in a liberal arts degree was not significantly associated with an increase in the frequency with which one utilized reflective writing. The cumulative self-administered rating scale score was not significantly associated with reflective writing frequency.

Conclusion: These results show that students who take time off between college and medical school are more likely to write reflectively and thus may be more inclined toward the mindful practice of medicine. These students may have perspectives informed by additional real-world experiences that have been grounded in the broader context of adult life; thus, they are more inclined to view medical school through a different lens than those who came directly from undergraduate college. Self-rated reflectiveness alone, however, was not necessarily correlated to frequency of reflective writing, suggesting that reflective writing is not solely required for reflective ability. Research to investigate the impact of reflective writing during medical school is ongoing. Accordingly, medical schools admissions committees should consider the impact of “non-traditional” factors and reflective potential of applicants to recruit future introspective practitioners. Additionally, applicants may wish to consider additional experiences between graduating from college and starting medical school to add depth and nuance to their medical school experience and, by extension, cultivate life-long skills for their medical career.

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Psychiatric Disorders and Substance Use in Homeless Youth: A Comparison of San Francisco and Chicago

Ernika Quimby

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Background: Youth homelessness is a growing problem in the United States. The experience of homelessness appears to have numerous adverse consequences, including psychiatric and substance use disorders.

Methods: This study compared the frequencies of psychiatric disorders, including substance use, between homeless youth (18-24 years-old) in San Francisco (n = 31) and Chicago (n = 56). They were administered the Mini International Neuropsychiatric Interview (M.I.N.I.) to assess DSM-IV-TR diagnoses and substance use disorders.

Results: Eighty-seven percent of the San Francisco youth, and 81% of the Chicago youth met criteria for at least one M.I.N.I. psychiatric diagnosis. Nearly two-thirds of the youth in both samples met criteria for a mood disorder. Approximately one-third met criteria for an anxiety disorder. Thirty-two percent of the San Francisco sample and 18% of the Chicago met criteria for Antisocial Personality Disorder. Approximately 84% of the San Francisco youth and 48% of the Chicago youth met criteria for a substance-related disorder, and more substances were used by San Francisco youth.

Conclusion: Our hypothesis was supported: there were high rates of psychiatric disorders, including substance use disorders, in both cities. SF youth had more psychiatric concerns, including higher rates of dependence/abuse and a greater number/range of substances. Differences between cities were not statistically significant, which may be in part attributable to the limited sample size. Some differences are likely explained by Chicago’s greater degree of racial/ethnic segregation, larger size, and more numerous/localized centers. The alarmingly high rate of psychiatric disorders in homeless youth provides clear evidence that the mental health needs of this population are significant and not being met.

Acknowledgements/Disclosures: None.
Pritzker Medical Student Perceptions of the Integration of the First-Year Curriculum: A Qualitative Analysis

Katie Richards

**Mentor:** H. Barrett Fromme, MD, MHPE, Department of Pediatrics

**Background:** Students of the Pritzker School of Medicine were asked to complete a survey for the LCME for re-accreditation purposes by January 2012. When asked to rate the integration of content in the first year, only 67% of participants were satisfied with this aspect of their education. This study investigated what Pritzker students perceive about the meaning of integration and examples of integration or places to improve integration within the first-year curriculum at Pritzker.

**Methods:** Two separate focus groups, one for MS14 students and one for MS15 students, were conducted. The seven questions asked regarded the definition of integration, its benefits and negative consequences, and the integration of the first-year curriculum at Pritzker. The sessions were audio-recorded, transcribed and de-identified, and the recordings were then destroyed. A qualitative analysis was performed on the resulting comments to determine what the most common types of answers were to these questions. When appropriate, MS14 and MS15 comments were compared.

**Results:** 67% of comments about the definition of integration were about Course Design and Structure, while 33% of comments focused on the Student Learning Process. In terms of the benefits of integration, 61% of comments dealt with improved knowledge acquisition. 31% of MS15 comments on this question were about how integration could increase internal motivation, whereas the MS14 class had no similar comments. Focusing on ways they perceived the first-year Pritzker curriculum is integrated, 92% centered on Course Design/Structure, the majority of which were MS15 comments about content overlap between courses. In terms of the ways they perceived that the classes are not integrated, 71% of comments dealt with Course Design/Structure, focusing on problems such as unclear expectations or poor coordination in classes with multiple lecturers.

**Conclusion:** While Pritzker students perceive that the majority of integration is about employing the best course structure, there are still many aspects that make up integration. This variety of definitions of integration demonstrates that the original question was too general. This could explain why there was such an unexpected rating for the question concerning integration of the first year classes. Most students perceive that integration is beneficial as it improves knowledge acquisition. The majority of students perceive that the first-year curriculum is well-integrated in terms of content overlap and clinical application. They perceive that the curriculum could improve its integration by setting more clear expectations for each course and by having better communication among lecturers and between course directors.

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Costs of Participating in a Diabetes Quality Improvement Collaborative: Variation Among 5 Clinics

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Co-Authors: Robert Nocon, Brenna S. Hughes, MS2, Monica E. Peek, MD, MPH; Elbert S. Huang, MD

Background: Quality improvement collaboratives (QICs), which allow clinics to quickly test and implement interventions through the collective experience of participating organizations, have been introduced as one way to improve quality of care and reduce costs. While they have been proven clinically promising and societally cost-effective for chronic disease care, their adoption may be hampered if costs of QICs outweigh their benefits to individual clinics. Diabetes QICs, evaluated over ten years ago, warrant re-examination as the costs of following new care guidelines, sustaining quality improvement efforts, and adopting community-based strategies, in addition to new financial incentives, may all shift the cost-benefit balance associated with quality improvement.

Methods: We describe the costs of an ongoing diabetes QIC initiated in 2009 that links 6 clinics on Chicago's South Side. Costs were assessed from the perspective of participating clinics. The QIC incorporates recommended strategies to improve minority health, such as tailoring care for African-Americans and building community partnerships. The clinics are supported by a project team that includes physicians and project management staff. The clinics include a hospital-based clinic, an endocrinology clinic, and federally qualified health centers. Cost estimates were calculated from surveys completed by QIC leaders at each clinic regarding activities, personnel time, and purchases.

Results: Data were obtained from 5 of 6 clinics in the QIC. The average costs/year ranged from $14k to $39k. The average costs/year/diabetic patient ranged from $6 at the clinic with the largest diabetic population to $68 at the clinic with smallest. Over time, the costs/year changed between year 1 (range across clinics: $11k-$35k), year 2 ($16k-$45k), year 3 ($12k-$39k), and year 4 ($13k-$37k) of the QIC. In terms of QIC activity type, the average breakdown of resource allocation included patient directed interventions (range across clinics: $8k-$33k), provider training ($0-$15k), delivery system redesign ($196-$12k), community engagement ($244-$25k), collaborative meetings ($4k-$13k), local QI meetings ($10k-$33k), information support ($0-$9k), and other activities ($832-$58k). Other activities generally included administrative duties related to the QIC that could not be attributed to specific QI initiatives. In terms of personnel type, the breakdown of labor costs included physicians ($818-$37k), nursing ($4k-$51k), educators/CDEs/nutritionists ($0-$31k), social workers or case managers ($22-$1k), nonmanagerial administrative staff ($2k-$9k), and managerial administrative staff ($0-$4k).

Conclusion: QICs are costly, labor-intensive endeavors for clinics, although experiences are diverse over time and setting. Costs tend to peak in year 2 of the QIC; the subsequent decline in costs may be from clinics learning to implement QI more efficiently. Smaller clinics tend to have the highest QIC costs per patient, suggesting difficulty in scaling QIC efforts to size. The framework of modern QICs, with their geographic and population focus, may allow some clinics to better capitalize on shared patients, infrastructure, and community relationships to experience cost savings. The results offer practical information to clinics and policymakers examining QICs.

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Evaluating the Role of Key Learning Theories in ECHO: A Telehealth Educational Program for Primary Care Providers

Carmela Socolovsky

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**Background:** ECHO (Extension for Community Healthcare Outcomes) is a telehealth educational program that uses videoconference technology to train community-based primary care providers (PCPs) on the management of complex, chronic diseases. The main components of ECHO are didactics, case presentations, and case-based learning. ECHO was developed using the key principles of Social Cognitive Theory, Situated Learning Theory, and Community of Practice Theory.

In a prior study, we implemented an ECHO curriculum to improve management of resistant hypertension. The goals of the current study were to determine the extent to which the learning theories served as the foundation of the ECHO curriculum and identify opportunities to more effectively incorporate key principles of these theories into the ECHO program.

**Methods:** From November 2010 to April 2011 we conducted a pilot ECHO curriculum in collaboration with six Federally Qualified Health Centers (FQHCs) on Chicago’s Southside. We then conducted semi-structured interviews with the nine clinicians who participated in the pilot curriculum. The key principles of the three learning theories served as the basis for interview questions to assess the extent to which these tenants were incorporated into ECHO-Chicago. A community-based PCP assisted with question development and manuscript preparation. We analyzed the interview transcripts using Directed Content Analysis.

**Results:** Transcript analysis supported the contention that our pilot ECHO curriculum reflected the key principles of the learning theories. Consistent with Social Cognitive Theory, participants reaffirmed they believed that the benefits of participation in ECHO outweighed the cost of attendance, stating “In here, it would take me about 6-7 months [to get a referral] if they don’t have insurance to get to a cardiologist. And now, this way, Monday [day of sessions] I’m going to...know what to give the patient.” Similarly, PCP comments suggested that peer-to-peer interaction built a community of learners and provided positive reinforcement from a disease expert, tenants of Situated Learning Theory and Community of Practice Theory. Participant G expressed, “I’ve enjoyed being able to see the participants from the different sites, to hear their questions. When they present their patients, I say, ‘Oh, okay I’ve had a patient like that’ or ‘that’s a good question. I’ve never thought about that aspect before.”

Conversely, participant comments also identified several opportunities to enhance ECHO-Chicago. Several individuals requested a printed copy of the case presentation so they could follow along more easily; provider E explained: “It’s hard for me to follow unless I actually have something written in front of me... Otherwise, I tend to just sort of let my mind wander.” Additionally, participant D felt motivation would be enhanced if participants received recognition for their participation in ECHO: “If you spend all this time learning about it, then you should be able to get a certificate...to show that you’ve done this and that you’re more educated.”

**Conclusion:** Our results indicate that ECHO indeed reflects the key tenants of Social Cognitive Theory, Situated Learning Theory, and Community of Practice Theory. Several aspects of our ECHO curriculum can be improved by more complete application of these learning theories.

**Acknowledgements/Disclosures:** None.
Scientific Investigation in Basic Sciences
TBX5 Drives Scn5a Expression to
Regulate Cardiac Conduction System Function

David Arnolds, PhD

**Mentor:** Ivan Moskowitz, MD, PhD, Departments of Pediatrics, Pathology, & Human Genetics

**Co-Authors:** Scott Smemo, PhD; Ozanna Burnicka-Turek, PhD; Malou van den Boogaard, PhD

**Background:** Cardiac conduction system (CCS) disease is common with significant morbidity and mortality. Key transcriptional mediators of fast conduction in the ventricular conduction system are currently undefined. Furthermore, the molecular logic underlying the recent association of SCN10A with cardiac conduction system function in genome wide association studies (GWAS) is not understood, as SCN10A has no known role in the heart. The gene product of the neighboring SCN5A gene, NaV1.5, however, is the major cardiac sodium channel. We hypothesized (1) that TBX5 regulates transcriptional networks required for fast conduction in the ventricular conduction system, and (2) that TBX5 regulates SCN5A expression via an enhancer at the SCN10A locus, providing a molecular explanation for recent GWAS results.

**Methods:** Ventricular conduction system (VCS) specific deletion of Tbx5 was achieved by administering tamoxifen to Tbx5minKCreERT2 transgenic mice. Ambulatory telemetry ECG analysis was performed for 24 hours. Electrophysiology studies were performed in anesthetized mice. Tbx5-responsive enhancers were identified using evolutionary conservation and published ChIP-seq studies. Luciferase studies were performed in HEK-293T cells. Mouse transient transgenic embryos were created using enhancer-Hsp68-LacZ fragments or LacZ-modified BACs. BAC modification was performed using the RedET recombination system. 4C-seq was performed using chromatin purified from adult mouse hearts. mRNA-seq was performed using left ventricular samples from patients who received LVADs or from non-implanted donor hearts, as well as right atrial tissue from patients undergoing surgery to repair congenital heart disease.

**Results:** Deletion of Tbx5 from the mature murine ventricular conduction system resulted in significant increases in the P-R, QRS, A-H, H, and H-V intervals, demonstrating slowed conduction in the absence of Tbx5. This was associated with decreased expression of key mediators of fast conduction, including the sodium channel NaV1.5 (encoded by SCN5A) as well as the gap junction connexin 40. Tbx5-responsive SCN5A enhancers were identified, including one located in SCN10A that harbors a SNP [rs6801957] associated with functional differences in P-R and QRS intervals in GWAS. Deletion of these enhancers resulted in decreased cardiac Scn5a expression using a BAC reporter strategy. 4C-Seq analysis verified physical interaction of the enhancer located within SCN10A with the SCN5A promoter. The minor allele at rs6801957 is associated with conduction slowing and disrupts a core TBX5 binding site; we demonstrate by mRNA-seq using human cardiac tissue that the minor allele at rs6801957 is associated with decreased SCN5A expression.

**Conclusion:** Our results demonstrate that TBX5 is required for fast conduction in the ventricular conduction system and identify key targets of TBX5 that may mediate this effect, including the sodium channel NaV1.5 and the gap junction Cx40. We further identify key SCN5A enhancers that are regulated by TBX5, including one located within the SCN10A locus. Variation at this locus is associated with variation in SCN5A expression levels in human cardiac tissue, providing a molecular explanation for the association of genetic variation at SCN10A with cardiac conduction system function.

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DNA Resection Proteins Sgs1 and Exo1 are Required for G1 Checkpoint Activation in Budding Yeast

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**Co-Authors:** Andrew Truman, PhD

**Background:** Cellular DNA is constantly exposed to endogenous and exogenous insults, often resulting in damage. The most deleterious type of damage is the chromosomal double strand break (DSB), which can lead to translocations and loss of genetic information, thus causing a variety of severe diseases. To maintain genomic integrity, cells activate the DNA damage response (DDR), which is a set of coordinated pathways that promote DNA repair while protecting the cell from further damage. An essential component of the DDR is cell cycle arrest, which delays progression through the cell cycle and allows for repair of the damage prior to replication. This arrest occurs at checkpoints that are located in strategic phases of the cell cycle: G1, S, and G2/M. Saccharomyces cerevisiae, also known as budding yeast, is commonly used as a model for studying DNA damage repair and cell cycle arrest in eukaryotes. The high level of conservation of the DDR pathway in eukaryotes makes findings from one organism appreciably applicable to others. Furthermore, there are two important advantages of employing budding yeast as our model organism. First, the genome can be easily manipulated because homologous sequences readily recombine in yeast. Secondly, the presence of haploid and diploid states in the cell cycle make the study of recessive and dominant phenotypes convenient.

**Methods:** Yeast strains used were constructed in the S. cerevisiae W303 background and plasmids were grown in Escherichia coli. Other techniques employed include the G1-checkpoint activation assay (alpha-factor/Noc Trap Assay), PCR, DNA sequencing, Western blot analysis, β-galactosidase assays, cell viability/DNA damage sensitivity growth assays, and light microscopy.

**Results:** Although DNA resection is necessary for initiating damage-induced cell cycle arrest in G2, no role has been assigned to it in the activation of G1 checkpoint. Here we demonstrate for the first time that the resection proteins Sgs1 and Exo1 are required for efficient G1 checkpoint activation. In G1-arrested cells, we find that the phosphorylation of histone H2A in response to DNA damage is independent of Sgs1 and Exo1. In contrast, Sgs1 and Exo1 are required for several damage-induced activities that include the recruitment of the single stranded DNA-binding protein, Rfa1 to the DSB sites; phosphorylation of the DDR effector kinase, Rad53; cell cycle arrest and expression of RNR3, which catalyzes dNTP synthesis. Furthermore, we showed that checkpoint activation in G1 requires the catalytic activity of Sgs1. Thus indicating that the DDR pathway depends on the DNA resection ability of Sgs1 as opposed to its other functions.

**Conclusion:** Our findings suggest that DNA resection is necessary for activation of the G1 checkpoint. This contrasts to the predominant impression in the field that resection plays a minimal role in G1. In addition, it indicates that the G1 checkpoint activation mechanism is similar to the well-studied G2/M checkpoint. Consequently, findings from decades-worth of G2/M studies in yeast can now be applied to G1. This is particularly relevant because human cells are primarily in G1, thus making G1-focused studies in yeast more applicable to the understanding of genetic diseases that afflict humans.

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OPG Deficiency Results in Disruption of Posterofrontal Suture Closure in Mice: Implications in Nonsyndromic Craniosynostosis

Maureen Beederman

**Mentor:** Russell Reid, MD, PhD, Department of Surgery, Section of Plastic & Reconstructive Surgery

**Co-Authors:** Stephanie H. Kim, PhD; M. Rose Rodgers, MA; Tong-Chuan He, MD, PhD

**Background:** Craniosynostosis, or the premature fusion of one or more cranial sutures, is a condition that affects approximately 1 in 2,500 live births worldwide. Much research on this topic has previously shown that osteoblasts are implicated in the complex mechanisms that lead to early suture fusion. Despite the concept that proper bone formation and remodeling involve an interplay between both osteoblasts and osteoclasts, relatively little is known about the role of osteoclasts in suture fusion. Osteoclasts are predominantly regulated by TNF-alpha superfamily members, receptor activator of NF-κB (RANK) and RANK ligand (RANKL), both of which lead to osteoclast differentiation, activation, and survival, as well as osteoprotegerin (OPG), a soluble inhibitor of RANK. Past work from our laboratory suggests that the RANK-RANKL-OPG pathway plays a role in patients with craniosynostosis. Our work further examines the role of OPG in this process using knockout technology.

**Methods:** All animal studies were approved by the University of Chicago Animal Care and Use Committee (IACUC). To investigate the role of OPG in suture homeostasis, wild-type, OPG+/-, and OPG -/- mice were bred and imaged by serial microCT scans at 3, 5, 7, 9, and 16 weeks. Suture density measurements and craniometric analysis were performed using Amgen image analysis software at these same time points. Posterofrontal sutures were harvested from mice after the Week 16 timepoint and analyzed via histochemistry.

**Results:** MicroCT analysis of the posterofrontal suture reveals reduced suture fusion in mice deficient in OPG when compared to wildtype (WT) and heterozygous littermates. Specifically, OPG deficiency resulted in a statistically significant decrease in suture bone density in knockout mice, with bone density averages of 979, 1124, 1301, and 1203 Hounsfield Units (HU) at Weeks 5, 7, 9, and 16, respectively. This is in contrast to WT mice, with average bone density values of 1272, 1544, 1690, and 1545 HU for these same time points. Unlike suture-containing bone, there was no reduction in the density of nonsuture-containing calvarial bone between WT and OPG KO mice. Histochemical staining of cryostat suture sections supports these microCT findings. Finally, the decline in suture fusion in OPG/- mice led to statistically significant craniometric differences in these mice. OPG KO mice have reduced anterior-posterior skull distance at all timepoints, and an increased interorbital distance at the Week 16 timepoint, further pointing to the role of osteoclasts in cranial development.

**Conclusion:** Our data from OPG knockout mice suggest that perturbations in the expression of OPG and subsequent changes in osteoclastogenesis lead to alterations in cranial and suture morphology. Osteoclast activation and maintenance via RANK/RANKL/OPG signaling plays an important role in cranial suture biology and cranial morphology in the murine posterofrontal suture. Further studies focusing on osteoclast biology in diseased and patent human suture samples are warranted.

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Role of Ets-1 in Coronary Vasculogenesis

Ankit Bhatia

Mentor: Eric Svensson, MD, PhD, Department of Medicine, Section of Cardiology

Co-Authors: Gene Kim, MD; Saoirse McSharry

Background: Coronary artery disease is the leading cause of mortality in the US with an estimated 400,000 deaths in 2007. To this point, the majority of therapies for CAD have been directed at either: (1) mechanically alleviating arterial blockages via stent placement/angioplasty, both of which have high rates of restenosis, or (2) providing alternative perfusion conduits via bypass grafting, an invasive procedure associated with significant morbidity and mortality. The growth of collateral coronary vessels to supply ischemic myocardium is a well-documented yet poorly understood phenomenon in CAD that provides glimpse into a potential novel therapy: “Coronary Angiogenic Therapy”, the induction of growth of new coronary vessels to treat CAD. Such a therapy is currently limited by our understanding of the molecular mechanism of coronary vasculogenesis. The Ets transcription factors are known to be involved in a broad spectrum of biological processes including cell growth and differentiation. Through previous study, our group has demonstrated that Ets-1 knockout mice exhibit a near uniform lethality between day 0 and 3 after birth. We observed left ventricular systolic dysfunction and a reduction in capillary density/coronary vessel plexus within their myocardium, pointing to vital nature of Ets-1 in coronary vasculogenesis. This study aims to further elucidate Ets-1’s role in coronary vascular development.

Methods: In this study, staged embryos of wild type and Ets-1-/- mice were generated from timed pregnancies and harvested at time points of 12.5 (E12.5), 14.5 (E14.5), and 16.5 (E16.5) days and genetically identified via PCR. Tissue sections were then fixed and snap frozen for subsequent transverse cryosectioning. Cardiac tissues sections were then stained with PECAM-1 and visualized under immunofluorescence to assess for coronary vascular density. E14.5 WT and Ets-1-/- cardiac tissue was also stained with Dll4 (arterial marker) and EphB4 (venous marker) to assess for arterial/venous density under IF. Finally, E14.5 WT and Ets-1-/- tissue samples were stained with Anti-phosphohistone H3, marker for mitosis, and TUNEL, marker for apoptosis, and quantified/normalized to number of endothelial cells to assess for endothelial proliferation and death.

Results: At time-points E12.5 and E14.5, a significant reduction in endothelial capillary density, specifically in sub-endocardium, was observed in Ets-1-/- hearts versus WT. Furthermore, Ets-1-/- hearts had a significant reduction in both arterial and venous myocardial density at E14.5 (n=10), again specifically in sub-endocardium. Finally, WT heart were shown to have a significantly increased mitotic index versus Ets-1-/- (n=10) with p=0.004, however no significant difference was noted in apoptotic index (n=10) with p=0.09.

Conclusion: Together, in the framework of prior data revealing reduced myocardial capillary density in Ets-1-/- mice hearts at birth, our data suggests Ets-1 is essential for the migration of sub-epicardial coronary vascular precursors and is highly expressed at time-points E12.5 and E14.5. Loss of Ets-1 leads to loss of both arterial and venous endothelium in the sub-epicardium. Ets-1 is also associated with increased coronary endothelial proliferation, but appears to play no significant role in endothelial apoptosis.

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Cerebrospinal Fluid Biomarkers in Spinocerebellar Ataxia

Ashley Brouillette

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Co-Authors: Gülin Öz, PhD

Background: Neurodegenerative diseases are chronic disorders that are characterized by progressive death of specific nerve cells in otherwise healthy individuals, leading to a gradual loss of normal brain function. SCA1, 2, and 6 are autosomal dominant diseases, and MSA-C is a sporadic disease, each characterized by progressive gait ataxia, hand incoordination, dysarthria, and in many cases, a variable pattern of other progressive neurological deficits. Neurodegenerative diseases, including the spinocerebellar ataxias (SCA) would benefit from the identification of reliable biomarkers that could serve as disease subtype-specific and stage-specific indicators for the development and monitoring of treatments.

Methods: We analyzed the cerebrospinal fluid (CSF) level of tau, alpha-synuclein, DJ-1, and glial fibrillary acidic protein (GFAP), proteins previously associated with neurodegenerative processes, in patients with the autosomal dominant SCA1, SCA2, and SCA6, and the sporadic disease multiple system atrophy, cerebellar type (MSA-C) compared with age-matched controls. We estimated disease severity using the Scale for the Assessment and Rating of Ataxia (SARA).

Results: Most proteins measured trended higher in disease versus control group, yet did not reach statistical significance. We found the levels of tau in both SCA2 and MSA-C patients were significantly higher than control. We found that alpha-synuclein levels were lower with higher SARA scores in SCA1, and tau levels higher with greater SARA in MSA-C, although this final correlation did not reach statistical significance after post hoc correction.

Conclusion: Our results have indicated differences in the trends of biomarker levels in different related neurodegenerative diseases, although additional studies with larger sample sizes are needed to improve the power of these studies and validate the use of CSF biomarkers in SCA and MSA-C.

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Seasonal Allergic Rhinitis Affects Sinonasal Microbiota

Christopher Choi

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Co-Authors: Valeriy Poroyko, PhD; So Watanabe, MD, PhD; Duo Jiang, BS; James Lane, BS; Marcella deTineo, BSN; Fuad M. Baroody, MD; Robert M. Naclerio, MD

Background: Allergic rhinitis is a risk factor for contracting acute rhinosinusitis. One way allergic rhinitis could predispose to acute sinusitis is by altering the balance of microbial flora in the sinonasal tract, allowing pathogens to grow preferentially. Notably, 60% of cases of diagnosed acute bacterial sinusitis do not grow bacteria by current, culture-based laboratory tests. Recent advances in microbial community profiling allow for characterization of these cultivation-independent bacterial species.

Methods: We performed a parallel observational study of healthy adults with seasonal allergic rhinitis (SAR) (grass or tree, n=20) or non-allergic subjects (n=19). Microbiota specimens were obtained by endoscopy from the middle meatus and vestibule prior to and during the relevant season and analyzed by Terminal Restriction Fragment Length Polymorphism analysis. Differences in bacterial microbiota were assessed by standard ecologic measures of bacterial diversity. Quality of life and symptom scores were recorded, and nasal lavages for eosinophils were performed.

Results: SAR subjects had increased nasal symptoms in season, impaired disease-specific quality of life, and increased nasal eosinophils, compared with no changes in non-allergic subjects. During the season, SAR subjects had a significantly greater variety of organisms in the middle meatus compared to non-allergic subjects (P<0.036) and increased bacterial diversity (Shannon index, P<0.013). We found a significant positive correlation between bacterial diversity in the middle meatus during the season and the nasal lavage eosinophil count of SAR subjects. There were no significant changes in the nasal vestibule (P>0.05, all comparisons).

Conclusion: The interaction of allergy and microbiota may affect the sinonasal physiology, with broad implications for several airway diseases. Characterization of the specific organisms involved using next generation sequencing may clarify the relationship between allergic inflammation and acute bacterial rhinosinusitis. This finding may help explain why allergic inflammation predisposes to ABRS.

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CT-Based Pulmonary Artery Measurements for the Assessment of Pulmonary Hypertension

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**Co-Authors:** Mardi Gomberg-Maitland, MD

**Background:** Pulmonary hypertension (PH) is a complex and fatal disease that is difficult to diagnose non-invasively. This study evaluated previously published CT-based vessel measurement criteria and investigated the predictive power and diagnostic ability of the main pulmonary artery diameter (MPAD) and the ratio of MPAD to aorta diameter (rPA).

**Methods:** The database for this study consisted of 175 PH patients, 16 non-PH patients, and 114 “normal” patients. The performance of previously published criteria, MPAD > 29 mm and rPA > 1, was determined. The relationship between vessel measurements and mean pulmonary artery pressure (mPAP) was evaluated through correlation and linear regression analysis. The ability of these measurements to discriminate between patients with and without PH was determined by receiver operating characteristic analysis.

**Results:** For discriminating between PH and “normal” patients, the sensitivity and specificity of MPAD>29mm was 0.89 (0.84-0.93) and 0.83 (0.76-0.90), respectively, and rPA>1 was 0.89 (0.85-0.94) and 0.82 (0.74-0.89). The sensitivity of MPAD was 0.81 (0.72-0.90) at a specificity of 0.95 and the sensitivity of rPA was 0.76 (0.66-0.85) at a specificity of 0.95 for separating PH and “normal” patients, but the specificity for both decreased when non-PH patients were included. For the combined PH and non-PH patient groups, the correlation between the vessel measurements and mPAP was significant but low, and the ability of the vessel measurements to predict mPAP was limited.

**Conclusion:** This study found that the sensitivity of previously published vessel criteria for identifying PH patients is high but the specificity may not be high enough for routine use in a clinical patient population.

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Differences in Aβ Release from Axonally vs. Dendritically Targeted Amyloid Precursor Protein

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Mentor: Sangram Sisodia, PhD, Department of Neurobiology

Co-Authors: Georgia Dolios; Rong Wang, PhD

Background: Alzheimer’s disease (AD), the most prevalent cause of dementia, is pathologically characterized by the presence of extracellular deposits of Aβ peptides in senile plaques. Aβ is a complex set of peptides generated by proteolytic processing of amyloid precursor protein (APP), encoded by a gene that is mutated, or duplicated in several pedigrees with familial forms of Alzheimer’s disease (Price and Sisodia, 1998). The processing of APP in nonneuronal cells has been extensively investigated (C et al., 2012), but information regarding the subcellular sites of Aβ production and release from neurons is limited. In this regard, synaptic activity increases Aβ release (Kamenetz et al., 2003; Cirrito et al., 2005) and high levels of released Aβ inhibits LTP induction at synapses (Kamenetz et al., 2003). Indeed, transient overexpression of APP in hippocampal slice cultures has revealed that Aβ released from either axonal or dendritic compartments leads to reduced spine density in neighboring dendrites (Wei et al., 2010). In this latter setting, neither the levels, nor identity of Aβ peptides released from pre- or postsynaptic compartments were assessed. We now document that neither endogenous rodent APP, nor axonally or dendritically targeted human APP are processed by α-secretase(s), but rather by β- and γ-secretases to generate an array of Aβ peptide-related species.

Methods: We created APP chimeras using the cytoplasmic targeting signals of NgCAM or LDLR to selectively target APP to axons or dendrites, selectively. We used lentiviruses encoding these APP chimeras to transduce primary hippocampal neurons to study the trafficking and processing of APP in neurons. The axon-to-dendrite polarization ratios of APP and APP chimeras were quantified using immunocytochemistry by confocal microscopy. We then examined APP processing and the nature of released Aβ peptides using biochemical approaches, including Western blot, S35-metabolic labeling and MALDI-TOF mass spectrometry.

Results: The APP chimeras were successful in creating polarized versions of APP. APP-LDLR was highly polarized to the surface of dendrites, while APP-NgCAM was highly polarized to the surface of axons in primary hippocampal neuron cultures. For the first time, we were able to quantify Aβ release from APP targeted to axons vs. to dendrites. We show that more Aβ is released from dendritically targeted APP compared to axonally targeted APP. MALDI-TOF mass spectrometry further characterized the profile of Aβ species generated by each chimera. We show that human APP processing generates mostly Aβ1-40 in primary neuron cultures. This is different than in non-neuronal cells, which generate mostly p3 (Aβ17-40). This is also different than rodent APP, which produces mostly Aβ11-40.

Conclusion: APP is processed in neurons, but little is known about the relative contributions of pre- or post-synaptic compartments to the release of Aβ peptides. To address this issue, we transduced primary neurons with lentiviral constructs expressing APP chimeras harboring targeting motifs from low density lipoprotein receptor (LDLR) or neuron-glia cell adhesion molecule (NgCAM) in order to polarize expression to either dendritic or axonal membranes, respectively. We now report that axonal or dendritically-targeted APP chimeras are subject to proteolytic processing in a very similar manner, but that the levels of secreted Aβ species are significantly higher in the medium of neurons expressing dendritically-targeted APP.

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Ultra-Long Term Stability of Single Units Using Chronically Implanted Multielectrode Arrays

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Mentor: Nicholas G. Hatsopoulos, PhD, Department of Organismal Biology and Anatomy

Co-Authors: Mukta Vaidya, BS

Background: The recording of neural activity from chronically implanted multielectrode arrays has become prevalent. Previous work has characterized the ability to isolate stable units over a time scale of weeks, but the extent to which populations of single-units remain stable over months to years is not clear. Here, we apply a method for tracking stable units over time to a collection of neural recordings from primary motor cortex over 18 sessions spanning 9 months.

Methods: Data used for this analysis were collected from a female rhesus macaque (Macaca mulatta) monkey that was implanted with a Utah 100-microelectrode array in primary motor cortex. Units were sorted online using a “hoop-sorting” algorithm. The behavioral task involved learning to control two dimensions of a robotic arm to perform a reach to grasp a sphere, to pull in back, and to drop it in a receptacle. The robot was composed of a 7 degree of freedom WAM arm attached to a 4 degree of freedom BarrettHand. The details of the method for tracking stable units have been previously published. It compares both the average waveform and the interspike interval histogram for a given units across days.

Results: Of the 137 neuronal units sorted on the first day, we found that 67% were stable through the first 15 days, 31% of units were stable through 47 days, 21% of units were stable through 106 days, and 8% of units were stable through 266 days. Moreover, stable units are more likely to remain stable: 75% of the units that are stable on day 47 survive the next 51 days.

Conclusion: Using a very conservative definition of stability, we were still able to identify a subset of the neurons that were stable over a time course of 9 months. The existence of long-term stability will aid the design of brain machine interfaces, since many of the decoding parameters should remain constant across days. We will also use this population of stable units to look at the effects of the learning on neuronal firing while the naïve subject is mastering a novel brain machine interface.

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SMAD Signaling Drives Heart and Muscle Dysfunction in a Mouse Model of Muscular Dystrophy

Jeffery Goldstein, PhD

Mentor: Elizabeth M. McNally, MD, PhD, Department of Medicine, Section of Cardiology

Background: Mutations in dystrophin or its associated proteins, the sarcoglycans lead to cardiomyopathy and muscular dystrophy in humans, mice, and flies. The dystrophin complex acts to stabilize the connection between sarcomeres, the plasma membrane, and the extracellular matrix. Disruption of the dystrophin complex in muscle causes cellular injury, dysfunction, cell death, and fibrosis. We previously showed that reduction of canonical TGFb/SMAD signaling improved walking and heart tube function in a Drosophila melanogaster model of muscular dystrophy. We now investigated whether SMAD signaling is elevated in muscular dystrophy in mice, and whether reducing signaling alters disease progression.

Methods: To test whether reducing SMAD signaling improves muscular dystrophy in mice, we introduced a heterozygous null mutation of SMAD4 into Sgcg mice (Sgcg/S4). We studied the phenotype of these mice by weight, cardiac and skeletal muscle physiology, histology, and the evans blue dye assay of membrane disruption. To determine whether the results are generalizable across different TGFb-reduction strategies, we treated a second cohort of mice with an antibody directed against TGFb.

Results: Compared to Sgcg mice, Sgcg/S4 mice showed increased body mass. Sgcg/S4 mice also showed improved cardiac function with increased fractional shortening and ex vivo muscle force. Sgcg/S4 muscle had reduced uptake of Evans blue dye, a marker of muscle membrane permeability but fibrosis was not changed compared to Sgcg muscle. The TGFb neutralizing antibody, 1D11, was less effective than SMAD4 mutation, possibly related to treatment duration or dose.

Conclusion: These data identify SMAD signaling as a therapeutic target.

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The Role of SMRT in Glucocorticoid Receptor-Mediated Gene Transcription

Xuan (Susan) Han

Mentor: Ronald Cohen, MD, Department of Medicine, Section of Endocrinology, Diabetes, and Metabolism

Co-Authors: Stelios Mantis, MD; Joshua Heiman, MS

Background: Clinically, excess glucocorticoids (GCs) have been implicated in the development of metabolic syndrome and its constellation of associated diseases. The presence of excess GCs in adipose tissue alone has been shown to cause metabolic syndrome in mice. These effects are mediated through the glucocorticoid receptor (GR), a member of the nuclear hormone receptor (NR) family. Upon translocation to the nucleus, NRs recruit coactivators and corepressors, such as silencing mediator of retinoid and thyroid hormone receptors (SMRT) to regulate gene transcription. The role of corepressors in GR action is currently unclear. SMRT may have a significant impact on lipid metabolism by interacting with GR and altering GR-regulated gene transcription.

Methods: Generation of Adipocyte Specific SMRT KO Mice: Floxed mice were generated in which the SMRT gene was flanked by two loxP sites. Floxed mice were backcrossed with adiponectin-Cre mice to generate mice in which SMRT was specifically inactivated in adipose tissue only.

qRT-PCR: Epididymal adipose tissue was harvested from WT and adipocyte-specific SMRT +/- mice. Total RNA was isolated and subsequently reverse transcribed to cDNA. qRT-PCR analysis was performed on cDNA samples.

Results: In WT mice, dex stimulates a greater than ten-fold increase in GILZ expression relative to non-treated adipose tissue, indicating that Gilz expression is mediated by GR. In the heterozygous SMRT +/- mice, there is a greater increase in expression of GILZ in response to dex compared to WT mice, suggesting that SMRT represses GR-mediated expression of GILZ. ChIP studies with LIPIN-1 show that SMRT is recruited to GR in the presence of dex, again suggesting that SMRT plays an important role in the regulation of glucocorticoid-stimulated gene transcription. In adipocyte-specific SMRT +/- mice, GILZ and LIPIN-1 are both expressed at greater levels relative to WT mice without any additional dexamethasone treatment. There is a 2.90 fold increase in GILZ expression and a 1.59 fold increase in LIPIN-1 expression in adipocyte-specific SMRT +/- mice relative to their WT counterparts.

Conclusion: Conclusions are pending final data - more gene expression studies need to be done using the adipocyte-specific SMRT +/- mice. Preliminary studies suggest that expression of GRE-containing genes is higher in adipocyte-specific SMRT knockout mice than in non-specific SMRT knockout mice.

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Assessing Residual Confounding in Heritability

Christopher King, PhD

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Background: The variation in a trait explained by SNPs genotyped via arrays or sequencing can be estimated by mixed models, but this method relies on the assumption of no residual confounding by population structure. Theory and previous empirical results suggest that standard adjustments for population structure may fail for rare SNPs.

Methods: We develop an estimating framework for the extent of residual confounding using pedigrees. We present both a control-function (CF) like estimator and a differences-in-differences (DD) estimator. Briefly, we regress the trait on the offspring genotypes and untransmitted parental alleles; untransmitted alleles should have no causal effect but have the same confounding as transmitted alleles. Alternatively, the offspring genotype of a heterozygous parent is exogenous variation which allows an instrumental variable estimate of the unconfounded SNP effect, which can be contrasted with the naïve effect. We test the validity of the estimators in simulation. We apply the estimators to 363 complete parent-offspring trios from the T2D-Genes whole-genome sequencing project of 20 prospectively sampled Mexican-American families. We examine several metabolic traits: fasting glucose, LDL cholesterol, total cholesterol, serum triglycerides, BMI, waist-hip ratio, systolic BP, diastolic BP.

Results: Simulation studies reveal that both the DD and CF estimators are valid under the null and consistent under the alternative. However, naïve computed variances of the DD estimate are incorrect and require bootstrap correction. Both estimators have low power for simulations like our real data and plausible values of heritability. In the T2D-Genes data, we are unable to demonstrate a significant effect of residual confounding for rare or common (5% MAF threshold) SNPs on heritability estimates. We do not find any Bonferroni-adjusted significant confounding of common SNP effects.

Conclusion: Family based studies can be used to empirically test the validity of population structure adjustment strategies by contrasting the extremely robust but highly variable estimates drawn from Mendelian variation among offspring to the more precise but potentially biased estimates comparing across families. In a small genome-wide sequencing study we do not find statistically significant evidence of confounding of the total heritability or of single SNP effects.

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Emotional Contagion is Required for Pro-Social Behavior in Rats

Teresa Murray

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Background: Emotional contagion, the capacity to resonate with another’s distress, plays a key role in empathically-motivated pro-social behavior. Emotional contagion relies on evolutionarily conserved neural structures, and has been demonstrated in many species, including rodents. In the helping behavior test, free rats act pro-socially by opening a restrainer door to release a trapped cagemate. Here we sought to determine whether emotional contagion contributes to this behavior by blocking the distress of either the free or the trapped rat by administration of midazolam, a benzodiazepine anxiolytic.

Methods: Male Sprague-Dawley rats, housed in pairs, were used in a helping behavior paradigm. One rat from each pair was designated the free rat based on boldness testing. Free rats were placed in arenas containing a restrainer in which either a trapped cagemate or chocolate chips were placed. Free rats could release their cagemate or access chocolate by opening the door of the restrainer. During the experiment, either the free or trapped rat was injected with one of two doses of the anxiolytic benzodiazepine, midazolam (MDZ), or with saline, administered 15 minutes prior to the behavioral testing session on each testing day.

For each opening event, the latency-to-opening was recorded. The total number of openings for individual conditions were summed for each day of testing. The mean latency to opening and the number of openings were compared between experimental conditions.

Results: The administration of MDZ to trapped rats led to significantly fewer door-openings when compared to trapped rats who were treated with saline (t-test, t=2.1, df=21, p<0.05). Similarly, the administration of MDZ to free rats reduced the number of rats who became openers. Only 1/15 rats injected with MDZ ever became an opener, in comparison to rats injected with saline (4/8, Fisher’s exact test, p=0.03). Despite a decrease in opening behavior when midazolam was administered to either the free or the trapped rat, midazolam did not impair rats’ ability to open a restrainer containing chocolate. Most rats injected with midazolam became openers (5/8, 62.5%), while free rats injected with saline did not open the restrainer to access chocolate chips, with only one rat of 8 becoming an opener (13%).

Conclusion: Communication of distress is critical for helping behavior to occur in this paradigm. Blocking the distress of either the trapped or the free rat via administration of midazolam reduces opening behavior for a trapped rat. However, midazolam does not decrease opening for chocolate, ruling out gross motoric or cognitive impairment as a cause of decreased opening behavior. This suggests that midazolam selectively impairs pro-social motivation through its ability to block distress in the helping behavior test. In conclusion, pro-social actions are motivated by emotional contagion in rats.

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The Role of GRK2 and β-Arrestins in Maladaptive Post-Infarction Ventricular Remodeling

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Background: Remote territory fibrosis following myocardial infarction (MI) is an important mechanism for the development of heart failure (HF). G protein-coupled receptor kinase-2 (GRK2) plays a key role in this process through uncoupling β-adrenergic receptor (β-AR) signaling in failing human cardiac fibroblasts (CF). β-arrestins are involved in β-AR uncoupling and have receptor-independent functions including activation of downstream signaling pathways that may be involved in CF-mediated fibrosis. This study investigates the role of GRK2 and β-arrestin in regulating CF biology in post-MI remodeling.

Methods: Adult Sprague-Dawley rats underwent left anterior descending coronary ligation to induce MI. Left ventricular (LV) function was assessed by echocardiography. Myocardial fibrosis was quantitated by histologic staining. LV CF were isolated and cultured. In cultured CF, β-arrestin expression was inhibited by siRNA-mediated knockdown and GRK2 activity was inhibited using adenoviral overexpression of GRK2 inhibitor, GRK2ct (Ad-GRK2ct). GRK2 activity was inhibited in vivo by intra-aortic injection of Ad-GRK2ct immediately following LAD ligation.

Results: There was a significant decline in LV function at 2 weeks post-MI which was present through 12 weeks [Fractional shortening: 0.35±0.01 vs. 0.52±0.01, p<0.01]. Remote territory (non-infarct area) fibrosis increased by 2 weeks post-MI [6±1% vs. 2±1% fibrosis, p<0.01] progressing by 12 weeks to 12% fibrosis [p<0.01], consistent with adverse remodeling. Collagen synthesis was significantly upregulated in isolated CF as early as 2 weeks post-MI [3132±115 vs. 1082±130 cmp/mg protein, p<0.01] which persisted through 12 weeks post-MI [2735±856 cmp/mg protein, p=0.02]. β-arrestin expression was increased 2-fold by 8 weeks post-MI and GRK2 activity was increased 1.4-fold by 12 weeks post-MI. These were associated with a 42% decrease in intracellular cAMP [p<0.05] and loss of β-AR agonist stimulated inhibition of collagen synthesis characteristic of normal CF [3969±1058 vs. 708±95 cmp/mg protein, p<0.01]. Knockdown of β-arrestin in CF isolated 8 weeks post-MI decreased transformation to activated myofibroblasts as measured by a 50% decrease in α-SMA expression [p<0.04] and inhibited collagen synthesis compared to scramble siRNA controls [1985±400 vs. 3431±51 cmp/mg protein, p=0.01]. Adenoviral mediated overexpression of GRK2ct, an inhibitor of GRK2, in CF isolated 12 week post-MI significantly decreased collagen expression and synthesis compared to null adenovirus (Ad-Null) control [1928±126 vs. 261±213 cmp/mg protein, p=0.02]. Intra-aortic injection of Ad-GRK2ct immediately following LAD ligation significantly decreased post-MI cardiac dysfunction; as measured by improved fractional shortening [0.42±0.01 vs. 0.30±0.02, p<0.01] and ejection fraction [72±1% vs. 57±2%, p<0.01] at 12 weeks post-MI vs. Ad-Null controls. Ad-GRK2ct also led to significantly inhibition of myocardial fibrosis at 12 weeks post-MI in both the infarct area [4±1% vs. 11±1% fibrosis, p<0.001] and the remote territory [4±1% vs. 12±1% fibrosis, p<0.001].

Conclusion: Remote territory fibrosis occurs by 2 weeks post-MI and increases over time. Uncoupling of β-AR signaling via increased GRK2 and β-arrestin appears to be an important mechanism of increased myocardial fibrosis, as intracellular cAMP is known to inhibit collagen synthesis. Targeted inhibition of β-arrestin and/or GRK2 and restoration of β-AR signaling in CF may represent novel approaches to inhibiting pathological fibrosis and adverse remodeling post-MI.

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Molecular Subtype-Specific Methylation of the Mir-29c Promoter in Breast Cancer Correlates with Basal-Like Pattern of Gene Expression

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Background: MicroRNA-29c (miR-29c) has been shown to have altered expression in several different cancer types, including gastric, leukemia, thyroid, and gliomas. Our lab previously identified miR-29c as a significantly down-regulated miRNA in basal-like breast tumors and demonstrated an association with cell invasion and sensitivity to chemotherapy. However, little is known about the genetic and regulatory factors contributing to the altered expression of miR-29c in breast cancer.

Methods: Expression of miR-29c was determined using qRT-PCR in breast cancer cell lines of the basal, luminal, and claudin-low subtypes. miR-29c promoter was located using CAGE-tag analysis and ChIP assays to determine transcription start sites and RNA polymerase II binding sites, respectively. Fluorescent In Situ Hybridization (FISH) was used to determine if there were differences in copy number of miR-29c. CpG islands were predicted using methylation software, and primers were designed to amplify those regions for sequencing after bisulfite treatment. The percent of methylated CpGs was compared to expression levels in breast cancer cell lines and results were validated using primary tumors in the TCGA dataset. Basal-like cell lines were treated for five days with decitabine, a chemotherapeutic hypomethylating agent and levels of miR-29c after treatment were measured.

Results: MiR-29c has lower expression in basal-like cell lines compared to claudin-low and luminal cell lines. FISH showed no changes in copy number of miR-29c between the different subtypes. We identified the promoter of miR-29c at the region upstream of the gene on Chromosome 1q32 and identified potential CpG islands in the promoter region. Bisulfite sequencing of DNA from breast cancer cell lines revealed a significant difference in percent of methylation between the different subtypes. The methylation of the promoter in basal, claudin-low, and luminal subtypes was 77.1%, 60.0%, and 16.6%, respectively (p=.002). The percent of methylation was inversely correlated with expression of miR-29c in the luminal and basal subtypes (R2=.68). An analysis of TCGA data for methylation at several CpG islands in the miR-29c promoter region in breast tumors confirmed a statistically significant mean difference of methylation of basal-like tumors versus Her2, luminal A and luminal B tumors. After treatment with decitabine, expression of miR-29c was elevated in basal-like breast cancer cell lines.

Conclusion: We have identified the location of the miR-29c promoter and determined that miR-29c is expressed lower in basal-like breast cancer cell lines and primary tumor samples in part because of a higher percentage of methylation at CpG islands compared to luminal breast cancer subtypes. This data suggests that epigenetic changes of the miR-29c promoter may be driving the lower expression of this miRNA in basal-like breast cancer, which may provide a potential therapeutic target to overcome the aggressive behavior of these cancers.

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Variants Affecting Exon Skipping Contribute to Complex Traits

Ellen Rebman

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Background: Alternative splicing is a common eukaryotic cellular mechanism that allows for the production of multiple proteins from one gene and occurs in 40%–90% of all human genes. Alternative splicing has been shown to be important for many critical biological processes, including development, evolution, and even psychological behavior. Additionally, alternative splicing has been associated with 15%–50% of human genetic diseases, including breast cancer; however, the precise mechanism by which genetic variations regulate this process remains to be fully elucidated. In this study, we develop an integrative approach that utilizes sequence-based analysis and genome-wide expression profiling to identify genetic variations that may affect alternative splicing. We also evaluate their enrichment among established disease-associated variations. Our study provides insights into the functionality of these variations and emphasizes their importance for complex human traits and diseases.

Methods: The overarching goal of this study is to discover and characterize the role that variants affecting alternative splicing may play in the genetic etiology of complex traits, which include a significant number of the common human diseases. Specifically, we hypothesize that single nucleotide polymorphisms (SNPs) in splicing regulatory elements can be characterized in silico to identify variants affecting splicing, and that these variants may contribute to the etiology of complex diseases as well as the inter-individual variability in the ratios of alternative transcripts. In this study we leverage high-throughput expression profiling to 1) experimentally validate our in silico predictions of skipped exons and 2) characterize the molecular role of intronic genetic variations in alternative splicing events in the context of complex human traits and diseases.

Results: We proposed that intronic SNPs function as genetic regulators within splicing regulatory elements and we were able to show that their associated exon skipping events could directly affect protein domains and structure. We found that SNPs that are predicted to affect exon skipping are significantly enriched among the sets of SNPs reported to be associated with complex human traits and diseases, thus identifying their likely biologic importance in the development of these phenotypic variables. Consistent with prior computational approaches that estimated that more than 50% of alternatively spliced regions in the human transcriptome affect protein interaction sites and more than 65% showed significant alteration in protein 3D structure, our study shows that 70% of skipped exons map to biologically functional regions.

Conclusion: We propose a systematic approach to integrate sequence, expression and genetics data (genotype/phenotype) in order to elucidate the impact of genetic variations on exon skipping and their importance in complex traits and diseases. Discerning genetic regulation of splicing is undeniably critical for understanding abnormal or physiological changes in alternative splicing since the number of currently characterized human splicing regulators cannot alone account for the tremendous number of splicing events known to occur in humans. We have shown not only that intronic SNPs are associated with exon skipping events but also that these SNPs are associated with complex traits, and that they are predicted to result in protein domain changes. While additional studies are needed to fully understand the role that genetic variation in splicing regulatory elements may play in alternative splicing, as well as how much alternative splicing-associated genetic variations contribute to common disease, this study provides support for continuing such investigations by outlining their very likely biological/phenotypic consequences.

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Ending Each Heartbeat: How do IKs Voltage-Gated Potassium Channels Activate So Slowly?

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**Background:** IKs voltage-gated potassium (Kv) channels are formed by KCNQ1 (Q1, also called Kv7.1 or KvLQT1) alpha-subunits and KCNE1 (E1, also called mink) beta-subunits. IKs channels pass the slow, repolarizing current that resets the myocardium at the end of each heartbeat. Mutations in Q1 or E1 can lead to many syndromes: Jervell and Lange-Nielsen, Romano-Ward, long-QT (LQT)-1, LQT-5, Beckwith-Weidman, familiar atrial fibrillation, short-QT. However, despite the pathophysiological relevance of IKs channels, the mechanism by which E1 subunits alter the biophysical parameters of Q1 to produce the characteristically slow current is the subject of active debate. Q1 subunits have 6 transmembrane (TM) spans: S1-S4 form the voltage sensing domain (VSD), while S5-6 form the channel pore. E1 is a member of the MinK-related family of peptides (MiRPs), which are single-TM spanning modules that can combine with various Kv channels to modulate gating, expression and sensitivity to drugs. Activation of Kv channels occurs when membrane depolarization induces positively charged residues in the S4 segment to move outward relative to counter-charges in the S2 and S3. This movement is then electromechanically coupled to opening of the S5-6 pore. E1 alters the operation of Q1 channels in a number of ways: slowing activation and deactivation kinetics, suppressing inactivation, increasing single-channel conductance, and altering ion-selectivity and pore-block. Given these effects, different investigators have hypothesized that E1 interacts with the pore, the VSD of Q1, or both to produce these effects. Two prior studies using indirect methanethiosulfanate (MTS) bonding rates yielded contradictory results (one arguing for changes in the operation of the pore, the other for the VSD, as the cause of slowed kinetics), and a recent fluorimetric study argued that E1 has both effects.

**Methods:** Here, we use direct, simultaneous real-time electrophysiological and optical measurements to study the movement of Q1 voltage sensors expressed in Xenopus Laevis oocytes. First, using cut-open oocyte voltage clamp, we recorded gating currents in Q1 channels. Next, direct correlation between kinetics of S4 motion and ionic current were recorded using site-directed fluorimetry (SDF) in both Q1 and IKs channel complexes.

**Results:** Gating current measurements have not previously been reported for Q1 channels and were ~28-fold slower than recorded from the canonical Kv channel, Shaker, at 40 mV and 28 °C. However, gating currents could not be resolved when Q1 was expressed with E1, indicating that the S4 movement is slowed considerably in the presence of the beta-subunit. To study the movement of the Q1 voltage-sensor we also recorded ionic currents and simultaneous environmentally-dependent changes in the fluorescence of tetramethylrhodamine appended to the S4 voltage sensor. We found that in IKs-channel complexes, both ionic current and voltage-sensor movement were ~40-fold slowed.

**Conclusion:** Direct correlation of the kinetics of S4 motion and ionic current indicated that slowing of sensor movement by E1 was both necessary and sufficient to determine the slow-activation time course of IKs-current. This novel work answered decades-old questions in the literature using direct evidence.

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Intrauterine Infection Induced Epigenetic Changes In the Fetus — Implications for Preterm Infant Morbidity

Wenjing Zong

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Co-Authors: Lei Lu, MD; Ellen Yu, MS

Background: Preterm birth is a major cause of infant morbidity and mortality, and is highly associated with intrauterine infection. Preterm birth caused by intrauterine infection is accompanied by an inflammatory response that is dependent upon TLR-mediated signaling, specifically through TLR2 and TLR4. Toll-like receptors (TLRs) are key pathogen recognition receptors of the innate immune system that recognize conserved structures expressed by microorganisms. However, little is known about how premature exposure of fetus to microbes results in perturbation of the homeostasis of the innate immune system and subsequent deficits in the infant’s long-term development. Epigenetics is the modification of DNA that leads to a stable change in phenotype without affecting the DNA sequence. One common epigenetic change is through gene methylation (represses gene expression) and de-methylation (enhances expression). We hypothesize that intrauterine microbial exposure increases intestinal injury through DNA methylation changes that regulate toll like receptors.

Methods: Pregnant mice received intrauterine inoculations with either phosphate buffered saline (PBS) or heat-killed E. coli (HKE) titrated to induce live delivery at term. Intra-peritoneal injection to mouse pups with PBS or lipopolysaccharide/platelet activating factor (L/P) was then performed as a secondary insult. This yielded four groups of mouse pups that were exposed to bacteria in utero and/or bacterial product in early life for analysis: 1. Control (PBS+PBS) 2. Experimental control (PBS+L/P), 3. Intrauterine exposure (HKE+PBS), 4. Intrauterine exposure with secondary insult (HKE+L/P). Mouse ileum was harvested from each group. Total RNA was extracted and gene expression was quantified. Similarly, genomic DNA was extracted and methylation level was measured for a panel of TLR signature genes.

Results: Our study shows that intrauterine infection decreases DNA methylation in genes involved in inflammatory response downstream of TLRs. Group 4 (HKE+L/P) had decreased methylation when compared to experimental control group 2 (PBS+L/P). Interestingly, gene expression profile showed lower expression of TLR2 across all groups when compared with control (PBS+PBS). When compared to the experimental control Group 2 (PBS+L/P), Group 4 (HKE+L/P) had increased TLR2 expression but decreased TLR4 expression. Group 4 also had decreased expression of Reg3b, an intestinal specific inflammatory marker.

Conclusion: Taken together, the methylation and expression analysis provide a complex picture of epigenetic regulation of inflammation in the mouse model of intrauterine infection. By itself, the methylation pattern suggests that intrauterine bacterial exposure activates TLR signaling. Gene expression analysis suggests that in utero exposure actually dampens the TLR2 and TLR4 signaling, as well as the local intestinal inflammatory response. More studies are needed to validate the relationship between methylation and expression, as well as exploring other epigenetic changes that may account for the expression pattern. In conclusion, this study shows that intrauterine infection suppresses TLR over-activation in innate immune development, possibly through DNA methylation.

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Scientific Investigation in Clinical Research or Social Sciences
Predicting Malignancy of Secondary Lesions with a Quantitative Computer-Extracted MRI-tumor Signature of Primary Lesions

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Background: Breast cancer patients may obtain dynamic contrast enhanced MR images (DCE-MRI) of a primary lesion pre- and post-biopsy. Post-biopsy images may reveal secondary lesions which require further biopsy. We aim to classify secondary lesions as benign or malignant given quantitative computer-extracted tumor signatures and hormone status of primary lesions, using pathology of the biopsy of the secondary lesion as “truth”.

Methods: IRB approved anonymized pathology reports, radiology reports and MR images were acquired through the Human Imaging Research Office at the University of Chicago. Primary lesions were manually isolated and computer segmented using fuzzy-c means. In-house software automatically calculated the features given the segmented lesion. There were 38 features grouped into categories of kinetics, morphology, texture, variance, size and hormone status. Estrogen receptor, progesterone receptor and HER2 status were acquired from pathology reports. Patients were separated by malignant and benign pathology readings on secondary lesions. AUC values were calculated from each feature. In addition a round-robin method was used to select features for creating a classifier based on linear discriminant analysis (LDA).

Results: 46 patients were included with 23 having malignant secondary lesions and 23 having benign lesions. AUC values were significant for variance of margin sharpness (0.84), time to peak at maximum variance (0.68), washout rate (0.65) and time to peak (0.65). The LDA classifier had an AUC of 0.78 with features including variance, effective diameter, progesterone receptor and variance in decreased rate.

Conclusion: In the task of classifying malignancy of secondary lesions using features of primary lesions, variance of margin sharpness and the LDA classifier had the highest AUC values. The collection of kinetic features had the highest percentage of significant results compared to other categories. Although the progesterone receptor was included in the LDA and BANN calculation, none of the individual hormone receptor features proved significant.

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The Predicted Impact of KDPI on Pediatric Renal Transplantation: Lessons Learned from the Intended and Unintended Consequences of Share-35

Christopher Chesley

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**Co-Authors:** William F. Parker, MD; J. Richard Thistlethwaite, Jr, MD, PhD

**Background:** Renal transplantation is the definitive therapy for patients in end stage renal disease (ESRD). Previous work has demonstrated that pediatric ESRD patients who receive a renal transplant achieve better developmental and cognitive outcomes compared to patients that receive dialysis. In October 2005, the United Network for Organ Sharing (UNOS) implemented Share-35, an allocation policy that gave children high priority for ideal deceased donor renal grafts (i.e., from donors <35 years). Recently, UNOS has suggested the use of the Kidney Donor Profile Index (KDPI) as the basis for graft allocation. We use a national transplant database to determine the consequences of the Share-35 policy change and contrast its successes with the potential unintended consequences of the KDPI system.

**Methods:** We analyzed pediatric waitlist data from the UNOS Standard of Transplant Analysis and Research data files. To understand the impact of Share-35, we analyzed the dataset between 9/30/2000 and 10/1/2010, comparing the 5 years that followed the policy implementation to the 5 years that preceded it. We examined changes in the demographics of the donors and recipients and assessed the impact of Share-35 on graft survival with respect to donor age and graft type. We then estimated the impact of KDPI-based allocation on the post Share-35 time period from 10/1/2005 and 9/30/2013. We calculated KDPI of grafts during this time and determined the distribution of KDPI across donor ages. Finally, we analyzed graft survival to determine how well KDPI reflected graft quality.

**Results:** Share-35 resulted in 41% more deceased donor renal transplants to pediatric recipients, but 32% less living donor transplants. Whereas approximately 30% of pediatric recipients received older kidneys (donor age >34 years) before the policy change, less than 2% of pediatric recipients received older kidneys after Share-35. Median time spent on the waitlist before transplant decreased from 204 to 150 days, and most of the improved time to transplant occurred within 6 months of being waitlisted. Despite a significant increase in HLA mismatching, there is no difference in overall graft survival after Share-35. Under a KDPI based allocation policy, we predict that nearly 20% (665/3619) of kidneys transplanted after Share-35 would not be available to pediatric ESRD patients. Of these unavailable grafts, 39% (256/665) are from donors aged <10 years. Though these young kidneys are considered inferior grafts by the KDPI system, grafts from donors age 1-9 years perform at least as well as grafts from donors age 10-34 years.

**Conclusion:** Share-35 was successful in increasing pediatric ESRD patients’ access to ideal deceased donor transplants. Though pediatric recipients receive less living donor transplants, Share-35 increased access to ideal deceased donors and led to shorter waitlist times. Even despite increased HLA mismatching, Share-35 represents a major improvement in pediatric renal allocation. However, the proposed switch to KDPI will significantly restrict access to many potential highly functioning renal grafts and fails to take into account the excellent performance of young renal grafts in pediatric recipients.

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Effect of Natalizumab on Cognition and Neurodegeneration in Relapsing-Remitting Multiple Sclerosis

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**Co-Authors:** Garrick Talmage, MS, MS2; Ashley Finch, BS; Adil Javed, MD, PhD

**Background:** Relapsing Remitting Multiple Sclerosis (RRMS) is a devastating neurological disease, characterized by altered permeability of the blood-brain barrier (BBB) resulting in lesions and neurodegeneration with a significant impact on cognition. The role of natalizumab, a recombinant monoclonal antibody thought to interfere with immune cell migration into the CNS, in preventing cognitive decline in MS and its effect on surrogate markers for neurodegeneration in MS has not been clearly established. Brain atrophy can occur early in the disease course of RRMS and lead to clinical disability and cognitive dysfunction, which may be delayed or reduced by natalizumab.

**Methods:** We conducted an ongoing, prospective, 96 week, single center, parallel group study of 20 patients with RRMS treated open-label with natalizumab. Analysis compared patients that started treatment less than two years after diagnosis with those starting treatment more than two years after diagnosis. Measures of neurodegeneration and cognitive function between the two groups were compared, with observations at baseline and follow-up after 24, 48, 72, and 96 weeks. Parameters measured included cognitive function indicated by Symbol-Digit Modalities Test (SDMT) z-scores, non-conventional MRI metrics estimated by FSL, and retinal nerve fiber layer thickness and macular volume as measured by optical coherence tomography (OCT). Statistical analysis was performed using SPSS 21.0 (SPSS, Chicago, IL, USA).

**Results:** To date twenty patients have undergone baseline exams. Nine patients have reached the 48 week follow-up examination, while five have completed the study at the 96 week follow-up. At the 48 week point, the change in thalamic volume correlated with cognitive decline as measured by verbal SDMT score after 48 weeks (R² = 0.471 P = 0.041), but not with hippocampal volumes (R² = 0.004 P = 0.885). The Percentage Brain Volume Change (PBVC) trended towards a greater decline from baseline to week 48 than week 48 to week 96, but there was not enough power at this point in the study to demonstrate statistical significance. Furthermore, Group 1 patients (<2 years since diagnoses) had greater improvement in SDMT z-scores at the 48 week point than group 2 (>2 years since diagnoses) which trended towards significance (P=0.106). Finally, global RNFL values for all patients did not worsen while on drug therapy for the patient who completed 96 weeks, but were lower than controls.

**Conclusion:** These findings suggest that treatment of RRMS with natalizumab early in the disease course may not only protect cognitive function, but lead to improved cognition. Furthermore, our findings correlated with previous reports of accelerated atrophy during the first year of natalizumab therapy, as noted by a more rapid decrease in percentage brain volume change from baseline to week 48 than week 48 to week 96. This is likely due to a reduction in inflammation that results in water volume loss, leading to a “pseudoatrophy” that is not likely a sign of pathology. Further investigation into brain atrophy as the study progresses is warranted to evaluate neurodegeneration in the absence of pseudoatrophy.

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Abnormal Nuclear Cyclin E Expression in Endometrial Glands of Patients with Recurrent Pregnancy Loss: Response to Vaginal Micronized Progesterone

Michelle Desjardins

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Co-Authors: Michelle Desjardins, MS4; Monica Willis, MD; Harvey J. Kliman, MD, PhD

Background: Cyclin E is a cell cycle regulator, which is highly expressed in proliferative endometrial glands but is normally absent after day 19. Objectives are to assess cyclin E in mid-luteal phase in a RPL cohort, determine whether progesterone down-regulates cyclin E, and improves subsequent pregnancy outcomes.

Methods: With IRB approval, 153 consecutive women with two unexplained miscarriages of <10 wks, seen between 07/2004-4/2012, were enrolled. An endometrial biopsy (EB) was performed 9-11 days after the LH surge. The EB was interpreted histologically and for cyclin E by IHC using the Endometrial Function Test. With elevated cyclin E expression (>20%), progesterone was prescribed, 100 mg q12h per vagina at LH +3 days. Subjects were offered a repeat EB on their first treatment cycle; progesterone was increased to 200 mg q12h if cyclin E did not normalize. Subsequently, pregnancy was defined as a +positive hCG at 4 weeks. Success rates (livebirths and ongoing pregnancies >10 wks) were compared prior and subsequent to intervention.

Results: There were 672 prior pregnancies; 85% were miscarriages. 84/153 had elevated cyclin E, of which 62 had no other endometrial findings, such as endometritis. 28/62 subjects had repeat EB on progesterone, of which 43% corrected. The 62 subjects with abnormal cyclin E had 271 prior pregnancies; these subjects had 88 subsequent pregnancies following intervention. The success rate was significantly higher after intervention, 6% (18/271) vs 67% (59/88). Conversely, the miscarriage rate was significantly lower, 85% (230/271) vs 31% (27/88).

Conclusion: Increased nuclear cyclin E in endometrial glands in mid-luteal phase can be down-regulated with progesterone. This preliminary data suggests that treatment with progesterone may improve subsequent pregnancy outcomes. A RCT is required to assess cyclin E as an indicator of endometrial-associated recurrent early pregnancy loss.

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Disagreement in the ICU — Which Caretakers Accurately Predict Patient Survival?

Michael Fenster

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Background: Accurate predictions of patient survival are important both to provide useful information to patients and families and to prevent futile efforts toward sustaining a dying patient. Our previous research has shown the utility in daily predictions of patient survival in the medical intensive care unit. In this study, we examined the accuracy of the predictions from each type of health care professional.

Methods: Over a period of 10 months, we asked healthcare providers in the MICU to predict whether or not each patient would survive to hospital discharge. These intuitions were collected from attendings, fellows, residents, and nurses on each day of MICU admission. We analyzed the accuracy of predictions by the type of provider for all patients who were admitted to the MICU for >72 hours. Days with discordant predictions — where one provider predicts survival and another predicts death before discharge — were analyzed to see which providers were most accurate.

Results: 411 patients were admitted for >72 hours during the study period and were included in the analysis. 31% of these patients did not survive to hospital discharge. There were discordant predictions on 142 patients (35%). On discordant days, providers correctly predicted outcomes 54.6% of the time. There was a trend towards fellows and residents being most accurate, correctly predicting the outcomes 62% and 59% of the time respectively. Attending physicians and nurses were least accurate (44% and 47% respectively), but these differences were not significant (Chi2, p=0.07). Nurses were most optimistic, predicting survival on 67.5% of discordant days while attending physicians were most pessimistic (32% predicted survival).

Conclusion: Caretakers disagreed on their intuitions of patient survival on over 1/3 of all patients hospitalized in the MICU for at least 72 hours. The amount of ICU experience did not predict which caretakers would be most accurate, with attending physicians less accurate than fellows and residents. Overall, caretakers could not accurately predict the outcomes of this subset of patients.

Acknowledgements/Disclosures: None.
Development of a Novel Tool for Measuring Upper Airway Inflammation

Jonathan Garneau

Mentor: Jayant Pinto, MD, Department of Surgery, Section of Otolaryngology

Co-Authors: Samuel Armato, PhD; Michael Ramirez, MS2; William Sensakovic, PhD; Adam Starkey, PhD

Background: It has been well documented in the literature that radiological assessment of computed tomography (CT) scans of patients with chronic rhinosinusitis (CRS) has its limitations in measuring symptom severity and quality of life. The most widely used scoring system is the Lund Mackay System that assigns a value of 0 (no inflammation), 1 (partial opacification), or 2 (full occlusion) to each sinus cavity based on extent of mucosal thickening. Although the Lund Mackay system has been lauded for its ease of use and low inter-observer variability among physicians, it has repeatedly demonstrated a weak correlation with symptom severity. Perhaps the lack of sub-grades within the score of “partial opacification” is responsible. However, we have developed a novel three-dimensional computerized tool to quantify mucosal inflammation of the paranasal sinuses. Based on our volumetric analysis, we created a “Modified Lund Mackay” scoring system with the hope of enhancing the current gold standard. Primarily, we evaluated our Modified Lund Mackay system by comparing it to the traditional Lund Mackay system in terms of correlation to patient symptoms. Secondarily, we aimed to use our volumetric analysis technique to investigate which paranasal sinuses have the greatest impact on overall symptoms in CRS.

Methods: A cohort of 55 patients were enrolled in a prospective, single center study. Each patient was presumed to have CRS and received CT imaging of the paranasal sinuses. Minutes before receiving their imaging studies, patients were asked to fill out two symptom severity questionnaires; Sinonasal Outcomes Test (SNOT-22) and Total Nasal Symptoms Score (TNSS). All patient scans were collected, anonymized, and processed for manual outlines. Using a computer outlining program, Abras, manual outlines of mucosal thickening of paranasal sinuses were created. Then, each outline was run through an 3-dimensional rendering algorithm to calculate percent opacification of each paranasal sinus cavity. Our Modified Lund Mackay (MLM) score was based on the volumetric analysis values. The Lund Mackay (LM) and MLM systems were compared using Mann-Whitney U test. The correlation with symptoms for both LM and MLM were examined by Spearman rank correlation values with SNOT-22 and TNSS symptom scores.

Results: The difference between overall LM and MLM scores (N=55) was found to be statistically significant (p=0.011). The spearman rank correlations of LM vs. symptoms were 0.018 and 0.114 for SNOT-22 and TNSS, respectively. The spearman rank correlations for MLM vs. symptoms were 0.202 and 0.181 with SNOT-22 and TNSS, respectively. None of these values had statistical significance (p<0.05). In terms of anatomical impact on symptoms, combinations of individual MLM scores for maxillary, anterior ethmoid and posterior ethmoid sinuses demonstrated statistically significant correlations with SNOT-22 and TNSS symptom scores.

Conclusion: Volumetric analysis scoring with MLM performed considerably better than the traditional LM system in terms of correlation with patient symptoms, although without statistical significance. In addition, volumetric analysis allowed us to observe that inflammation in maxillary and ethmoid cavities has the strongest correlation with symptoms, suggesting that an optimal scoring system may not be one that weighs all paranasal sinuses equally.

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Correlation Between Predicted to Observed Coronary Stent Expansion as Determined by Intravascular Ultrasound: Variance Between Stent Platforms and Impact of Lesion Characteristics

Vikrant Jagadeesan

**Mentor:** Sandeep Nathan, MD, Department of Medicine, Section of Cardiology

**Co-Authors:** Mark Gajjar, MD; Linda Lee, BA

**Background:** Intracoronary drug-eluting stents (DES) expand via balloon inflation within an arterial lumen to a pre-determined axial diameter for a given inflation pressure. In general, higher atmospheric inflation pressures yield increased DES axial diameters, up to a limit beyond which DES performance is compromised. Manufacturer-published data on predicted DES expansion is based on in-vitro testing. Actual expansion, during in vivo cardiac catheterization, may be dependent on other variables not controlled for in the in vitro setting. These may include differences in DES architecture, lesion characteristics, presentation acuity, co-morbidities, etc. The purpose of this study was to evaluate the relationships between these variables on DES expansion during percutaneous coronary intervention (PCI) via intravascular ultrasound (IVUS).

**Methods:** 46 total patients were retrospectively analyzed who had been treated at the University of Chicago catheterization laboratories by a single operator. Patients underwent PCI for the lesion of interest including pre-DES balloon inflation followed by DES deployment. Then, all DES underwent post-deployment imaging analysis with a Volcano EagleEye Platinum 20 MHz IVUS catheter. 1,652 IVUS frames were acquired and analyzed in 56 lesions after DES deployment. DES studied were Medtronic’s Endeavor (n = 32, 666 total mm) and Resolute (n = 12, 266 total mm), and Abbott Xience V (n = 12, 215 total mm) deployed at 16-22 atmospheres. Decisions regarding the particular DES, its size and dimensions, and peri-procedural clinical management were left to the discretion of the single operator in this study. Data recorded include plaque burden/area, and DES/vessel diameters and cross-sectional areas. Expansion deficit (ED, %), a calculated parameter, was defined as the percent difference between observed to predicted stented diameter.

**Results:** All DES, regardless of type, were less expanded than predicted (ED = -10.5%, p < 0.001) even though by IVUS, none were mal-apposed. Mean ED was highest in Endeavor vs. Xience or Resolute (-11.8% vs. -6.0% vs. -10.6%, p < 0.001). 98.4% of Resolute frames were under-expanded vs. 93.7% Endeavor frames and 80.4% Xience (p < .001). ED was greater in acute coronary syndrome (ACS) vs. non-ACS (-11.2% vs. -10.2%, p < .002), and left anterior descending artery (LAD) vs. non-LAD lesions (-12.07% vs. -8.07%, p < .0001). The highest ED (-12.05%, p < .001) was in 3.0 mm manufacturer-predicted DES. ED correlated with plaque burden for Endeavor (r = -0.267, p < 0.001) and Xience (r = -0.17, p < .01), but not Resolute (r = 0.006, p = 0.92).

**Conclusion:** Initial findings suggest that in vivo DES expansion tends to be less than manufacturer-predicted data based on in vitro testing parameters. This is observed even in the context of high atmospheric pressure deployment. Inter-stent architectural differences, lesion/vessel-specific variables, and individual patient clinical parameters appear to impact stent performance in vivo. These data have implications ultimately on stent selection/deployment and underscore the value of post-DES intravascular imaging.

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Ionizing Radiation Exposure Associated with Ejection Fraction Monitoring in Patients Undergoing Breast Cancer Treatment

Jeong Hwan Kim

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Co-Authors: Gillian Murtagh, MD; Karima Addetia, MD; Zoe Yu, MD; Amit Patel, MD; R. Parker Ward, MD; Victor Mor-Avi, PhD; Roberto Lang, MD

Background: Many chemotherapeutic agents for breast cancer are known to be cardiotoxic. Thus, it is customary to monitor ejection fraction (EF) of the patients receiving such treatments, either by transthoracic echocardiography (TTE) or multigated acquisition radionuclide imaging (MUGA). MUGA yields more reproducible data than TTE, but leads to ionizing radiation exposure of approximately 8mSV per scan. Patients receiving trastuzumab (TST) typically undergo up to 5 MUGA scans during the 1-year treatment period in addition to other diagnostic tests involving ionizing radiation. Thus, sequential EF assessments required with breast cancer treatment may amount to considerable radiation doses. This study aims to investigate whether breast cancer patients undergoing chemotherapy are exposed to ionizing radiation ≥50mSv/year from imaging and what proportion of the exposure comes from MUGA for the purpose of EF assessments.

Methods: Electronic records of 139 female patients diagnosed with breast cancer (age 53±12 yrs, 23 treated with TST) during 2010-2012 were reviewed. Estimated radiation dose (ERD) was used to calculate the radiation exposure associated with imaging procedures within 12 months of the first EF assessment.

Results: The majority of the patients (108/139, 78%) had at least one MUGA performed, while less than a third (31/139, 22%) had TTE only. The use of MUGA was most frequent in those treated with TST (20/23, 87%). Total ERD in the MUGA group was more than twice that in the TTE group (32±12 mSv vs 14±26 mSv, p<0.01 by unpaired t-test). In the MUGA group (N=108), 46 (43%) of subjects were exposed to 0-25mSv, 44 (40%) to 26-49mSv and 18 (17%) to ≥50mSv. Only 6% were exposed to ≥50mSv in the TTE group. Over a third (34±27%) of the total ERD in the MUGA group was due to EF assessment.

Conclusion: MUGA was used to monitor EF in the majority of breast cancer patients (78%). The use of MUGA was even more frequent in those treated with TST (87%). Those who underwent MUGA to monitor EF resulted in greater radiation exposure than those with TTE only. Given the considerable proportion of ionizing radiation exposure from EF monitoring (34%), the radiation exposure should be taken into account when the method of EF monitoring is chosen for any patient undergoing breast cancer chemotherapy. Techniques without radiation exposure, such as TTE or cardiac MRI, should be given strong consideration.

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Factors Affecting Wound Healing in Anterior Thigh and Groin Soft Tissue Sarcomas

Robert Kulwin

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Co-Authors: Tessa Balach, MD; Mark Cote, DPT, MSCTR; Terrance D. Peabody, MD

Background: The current management of soft tissue sarcomas consists of wide local excision, often in combination with radiation therapy and chemotherapy. Although these methods allow for limb-sparing resections, wound complications and their associated morbidity can complicate the course of treatment. While it has been established that overall rates of wound healing complications differ between anatomic sites, no study has addressed whether the risk factors for these complications also differ. This study was performed to determine the risk factors for wound healing complications in the proximal anterior thigh, and if there are benefits of soft tissue flap coverage.

Methods: The records of patients who underwent resection of soft tissue sarcomas of the proximal thigh at our institution from August 1, 1998 to May 30, 2012 were reviewed to evaluate for risk factors for wound healing complications. Age at surgery, greatest dimension of the excised specimen, immediate flap, preoperative or postoperative radiation therapy, preoperative or postoperative chemotherapy, wound healing complications, and additional surgical procedures to address the surgical wound were evaluated. A wound healing complication was considered to be major if an additional surgical procedure was required. Chemotherapy was categorized as none, preoperative (received preoperatively), or postoperative (received postoperatively only). Univariate and bivariate logistic regression models were used to determine which factors were associated with an increased frequency and risk of wound healing complication.

Results: The medical records of 59 patients (29 female, 30 male, mean age 59.8 ± 16.4 years) were included in the study. 22 patients (39%) developed a wound healing complication and 13 required an additional surgical procedure, 12 of which were related to a wound healing complication. Both preoperative (OR=3.9, p=0.04) and postoperative chemotherapy (OR 11.2, p=0.04) were found to be a significant risk factors for any wound healing complications whereas age (OR=1.0, p=0.77), greatest dimension (OR=1.1, p=0.22), immediate flap (OR=0.8, p=0.71), preoperative (OR=2.1 p=0.19) and postoperative radiation (OR=2.4, p=0.20), and were not predictive. Both preoperative (OR=6.8, p=0.02) and postoperative chemotherapy (OR=14.3, p=0.01) were also significant risk factors for major wound healing complication, whereas age (OR=1.0, p=0.94), greatest dimension (OR=1.1, p=0.25), immediate flap (OR=0.97, p=0.97), preoperative (OR=0.9 p=0.84) and postoperative radiation (OR=2.9, p=0.15) were not predictive. There were no additional risk factors identified with bivariate analyses.

Conclusion: Wound healing complications are a significant source of morbidity in patients with soft tissue sarcomas of the proximal anterior thigh. This retrospective review supports the hypothesis that risk factors for wound healing complications may vary between anatomic sites. Chemotherapy, in any stage of treatment, was found to be a significant risk factor for wound healing complications and additional surgery. Radiation therapy, though not statistically significant, was associated with an increased risk of wound healing problems. A larger, multicenter study may more accurately describe the wound healing complication risk profiles associated with individual treatment modalities on a site-specific basis.

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Multimodal Pain Management in Total Knee Arthroplasty: A Prospective Randomized Controlled Trial

Joseph Lamplot

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Co-Authors: Eric Wagner, MD; David Manning, MD

Background: Total knee arthroplasty (TKA) is one of the most successful medical procedures, but a critical and often suboptimal component of recovery is postoperative pain control. Adequate pain control allows faster rehabilitation, reduces complications and has been shown as the most important component of patient satisfaction. Frequently used, large doses of parenteral narcotics are associated with significant adverse effects. Multimodal analgesic protocols may improve postoperative pain control while decreasing associated adverse effects. We analyze the effects of a multimodal analgesic regimen on postoperative pain, function, adverse effects and satisfaction compared to patient-controlled analgesia (PCA).

Methods: 36 patients undergoing TKA at a single institution were randomized to one of two study arms. Multimodal group: Intraoperative: Periarticular injection before wound closure (30 cc 0.5% bupivacaine, 10 mg MSO4, 15 mg ketorolac) placed around posterior capsule in posteromedial and posterolateral soft tissues, synovium, pes anserinus and iliotibial band at Gerdy's tubercle Postoperative: Scheduled oxycodone 10 mg orally every 12h, tramadol 50 mg orally every 6h, ketorolac 15 mg parenterally every 12 h, hydrocodone 5 mg orally as needed and hydromorphone 1 mg parenterally as needed for rescue. Control (PCA) group: Intraoperative: No periarticular injection Postoperative: Hydromorphone PCA and hydromorphone 1 mg parenterally as needed. Preoperative and postoperative data were collected on post-operation days zero, one, two and at a three-week follow-up appointment for VAS pain score, narcotic consumption, medication-related adverse effects, time to physical therapy milestones, length of hospitalization and patient satisfaction score. Total narcotic usage was standardized and equianalgesic dosages determined. Physical therapy milestones included active straight leg raise, time until patient first gets out of bed, ambulation about the hospital room with or without assistance, ambulating 100 feet and ability to climb stairs.

Results: 36 patients were randomized into one of two groups, with 19 assigned to the multimodal group and 17 to the PCA group. During hospitalization, there was a difference in total narcotic consumption between the two groups, with 66.2±12.8 equivalents in the multimodal group compared to 150.4±35.8 in the PCA group (p<0.0004). Daily narcotic consumption was also lower in the multimodal group compared to the PCA group (p<0.007). Fewer patients in the multimodal group (16%) experienced narcotic-related adverse effects than the PCA group (94%) (p<0.01). VAS pain scores for pain at rest and during physical therapy were lower in the multimodal group compared to the PCA group for each day of hospitalization (p<0.0004 and p<0.001, respectively). At the three-week follow-up appointment, VAS scores for patients in the multimodal group were lower than the PCA group (p<0.05). Patients in the multimodal group performed better during postoperative physical therapy, reaching each measured milestone at an earlier time (p<0.01). Patients in the multimodal group reported higher satisfaction scores at all measured time points (p<0.01) and increased functional abilities at the three-week follow-up visit (p<0.01).

Conclusion: Multimodal pain management improves pain control, decreases narcotic consumption and opioid-related adverse effects, facilitates the achievement of early physical therapy milestones and improves overall patient satisfaction following TKA.

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Neurocognition and Clinical Features in Young Adults with Trauma and Gambling

Daisy Nie

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**Co-Authors:** Katherine L. Derbyshire, BS

**Background:** Prior studies have suggested that the rates of PTSD and childhood trauma are higher in disordered gamblers compared to the general population. Limited data exist, however, about the rate of trauma and its association with cognitive and behavioral measures in non-treatment-seeking young adults with gambling disorder.

**Methods:** We looked at non-treatment-seeking young adults (aged 18-29 years) participating in a longitudinal study on impulsivity who met DSM-5 criteria for gambling disorder. Gamblers who reported a history of trauma were compared with those who reported no trauma history on measures of gambling symptom severity, co-occurring disorders, impulsivity, and cognitive functioning.

**Results:** Among a sample of 46 non-treatment-seeking young adults with gambling disorder, 33% (n=15) reported a history of trauma. Disordered gamblers with a trauma history were more likely to use nicotine than those without (p=0.012), but otherwise did not have significant differences in co-occurring psychiatric disorders. Gamblers who experienced trauma reported higher average amounts of money gambled (p=0.027) and greater problems with self control (p=0.006). They also trended towards more severe gambling urges and behaviors. Cognitively, those with trauma showed greater difficulties with spatial working memory tasks.

**Conclusion:** Rates of trauma appear to be high among non-treatment-seeking young adults with gambling disorder. A history of trauma is associated with greater cognitive difficulties, poorer self control, and more severe gambling behaviors. These findings suggest that young disordered gamblers who have experienced trauma might benefit from unique strategies in management.

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Clinical Predictions of Death Prove Powerful Over 6 Month Period for MICU Patients

Daniel Reynolds

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**Co-Authors:** Michael Fenster, MS4; Moshe Prero, MD; Lea Redd, BA

**Background:** Adults that become seriously ill often require treatment in medical intensive care units (MICU's), and many of these patients will have a poor prognosis once in the MICU. Clinical predictions of survival from the MICU have long been thought to be a potential tool for physicians and families when faced with difficult decisions for MICU patients, although past studies have shown clinical predictions are often inaccurate. In our study, we sought to test the power of clinical predictions of death before hospital discharge for MICU patients for outcomes both in hospital and in a 6 month period following hospitalization.

**Methods:** We identified patients who were in the MICU for over 72 hours at The University of Chicago from March 2012 to December 2012. On each day of hospitalization in the MICU, each clinical caretaker (attending, resident, fellow, nurse) was asked “Do you think this patient will die in hospital or survive to be discharged?” We also consented patients for follow up in this study via a phone interview. Once discharged, patients were contacted at 1 month, 3 months, and 6 months to in order to determine if the patient was still alive. Moreover, we determined their level of impairment by measuring a Barthel Score via phone interview, with a score of less than 70 indicating impairment.

**Results:** We identified 413 patients who were admitted over a 9 month period in 2012 that were in the MICU over 72 hours. Of these, 132 patients (31.9%) died in hospital before discharge. The average age of patients in the MICU was 58.9 years, and there was no significant difference in age between those that died (61.19) and those that lived (59.17). Of the 204 patients who had at least one day with one prediction of death before discharge, only 53.4% died in hospital. A corroborated (more than one clinician predicted death on a single MICU day) raised the Positive Predictive Value of a prediction of death to 71.5%. Furthermore, a unanimous prediction (3 or more clinicians agreed) raised the PPV to 83.1%. Follow Up data was available on 176 patients, of whom 75% died in hospital. A corroborated prediction of death had a PPV of 93.6% for the outcome of death in hospital, and 100% of patients who had a corroborated prediction of death were deceased within 6 months. We are continuing to update our follow up data to include more patients as they respond to our study.

**Conclusion:** We have found that clinical predictions of death before hospital discharge can be valuable both in the immediate hospitalization period as well as in the 6 month period following hospitalization. While we have found that singular predictions of death before hospital discharge are not especially powerful, corroborated predictions and unanimous predictions of death are powerful in predicting in-hospital mortality. Furthermore, 100% of patients who had a corroborated prediction of death either died in hospital or were deceased within 6 months.

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ENVISIONED: 
Examining Vision Among Inpatients with Diabetes

Madeleine Shapiro

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**Background:** As patients are increasingly relied on to self-manage their complicated medical regimens, barriers to care must be determined and addressed. Early work has shown that vision may represent an under-recognized, independent risk factor for poor self management. Specifically, patients with diabetes who are at increased risk for eye disease and vision loss may have greater difficulty performing self-care tasks such as injecting insulin or checking blood glucose levels. Previous work has shown that almost one-third of general medicine inpatients fail a vision screening test. However, to date, no studies have specifically evaluated vision among hospitalized patients with diabetes. Therefore, our pilot aims to evaluate the prevalence of poor vision and characterize access to vision care for inpatients with diabetes.

**Methods:** Hospitalized adult general medicine inpatients were enrolled in an ongoing study of resource-allocation and quality of care. Vision was tested using the Snellen eye chart; sufficient vision was defined as at least 20/50 in at least one eye. Diagnosis of diabetes was determined based on self-report and/or chart review (hemoglobin A1C measurements). Participants completed a general survey about access to vision care, the Diabetes Empowerment Scale-Short Form, and the Diabetes Knowledge Test. Descriptive statistics were used to determine means and proportions. Chi-squared tests were used for categorical comparisons.

**Results:** Vision screenings were completed in 2298 participants, the majority of whom were female (56%) and African-American (78%), with a mean age of 53. Among the participants, 28% had diabetes (mean HbA1c 8.9, range 5.4-17.4) and 31% had insufficient vision. Participants with diabetes were more likely than those without diabetes to have insufficient vision (246/636, 39% vs. 415/1662, 25%; p<0.001). Significantly more participants with diabetes reported that they “think they need to see an eye doctor” (129/213, 61% vs. 312/618, 50%; p=0.01) and that they “have seen an eye doctor in the last year” (151/186, 81% vs. 331/460, 72%, p=0.02). Although 94% of participants believed that patients with diabetes should get a dilated eye exam at least once a year, only 51% have had one in the last year. Among the eight items on the Diabetes Empowerment Scale, a non-trivial proportion of participants reported discomfort with self-care and coping with stress. In contrast, participants commonly felt comfortable staying motivated and making the right care choices. As this is a pilot study, data collection is ongoing.

**Conclusion:** Our pilot study demonstrates that the prevalence of poor vision is higher among inpatients with diabetes than those without diabetes and access to vision care for these patients may be inadequate. Hospitalists should not miss the opportunity to identify inpatients with diabetes and refer them for guideline-recommended care. Particular attention should also be paid to improving patient empowerment in areas such as self-care and coping with stress. Future work should address possible hospital-based interventions to reduce these disparities and improve vision-related care for patients with diabetes both in the hospital and after discharge home.

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A Sense of Calling and Primary Care Physicians’ Satisfaction in Treating Depression, Anxiety, and Chronic Back Pain

Alexander Sheppe

Mentor: Farr A. Curlin, MD, Duke University & School of Medicine

Co-Authors: Ryan E. Lawrence, MD, MDiv; John D. Yoon, MD

Background: For primary care physicians, treating depression, anxiety, and chronic back pain can present frustrating challenges. These common conditions are often seen as complex, less concretely organic, chronically resistant to treatment, and diseases of difficult patients; repeatedly grappling with these challenges can lead to career dissatisfaction, burnout, and lower-quality patient care. Prior research has shown that when physicians see medicine as a calling, they experience significantly greater satisfaction treating smoking, alcoholism, and obesity, all classically common but difficult-to-manage conditions. To date, no study has examined if a sense of calling is correlated with greater physician satisfaction when treating depression, anxiety, and chronic back pain.

Methods: We mailed a confidential, self-administered survey to a stratified random sample of 1504 US primary care physicians (PCPs). Outcome measures were questions about how much personal satisfaction physicians experience when taking care of patients with depression, anxiety, and chronic back pain. Predictors were physicians’ demographic and religious characteristics, as well as whether they agreed or disagreed with the statement, “For me, the practice of medicine is a calling.”

Results: The overall response rate was 63%. PCPs were most satisfied treating patients with depression (78% experienced “some” or “a lot” of personal satisfaction), followed by anxiety (71%) and chronic back pain (42%, P<0.0001 for all comparisons). PCPs who view medicine as a calling were significantly more likely to experience “some” or “a lot” of satisfaction treating patients with depression (OR 2.5), anxiety (OR 1.8), and chronic back pain (OR 1.7, P<0.05 for all analyses). Additionally, PCPs who were older than 36 or identified as Hindu were significantly more likely to experience satisfaction treating patients with these conditions.

Conclusion: PCPs who are older than 36, identify as Hindu, or view medicine as a calling are significantly more likely to experience “some” or “a lot” of personal satisfaction when treating patients with depression, anxiety, and chronic back pain. It appears that older age, certain religious beliefs, and a sense of calling may serve as resilience measures against career dissatisfaction and burnout. This study, relevant to such fields of inquiry as medical education, physician burnout, and the doctor-patient relationship, calls for continued exploration of how these characteristics lead to greater physician satisfaction and ultimately better patient care.

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Comparison of Mental Status Scoring Systems for
Predicting Mortality in the Hospital

Linda Tien

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CO-AUTHORS Frank J. Zadravec, MPH; Brian J. Robertson-Dick, MD; Trevor C. Yuen; Matthew M. Churpek, MD, MPH, PhD

Background: Altered mental status is one of the most accurate predictors of mortality in hospitalized patients. Several scales exist to characterize mental status, including the AVPU (Alert, responds to Voice, responds to Pain, Unresponsive) scale, which is used in many early warning scores in the general ward setting. In addition, the Glasgow Coma Scale (GCS) and Richmond Agitation Sedation Scale (RASS) have both been validated in critically ill and trauma patients to detect mortality but their use is not well established in the general ward population. We sought to compare the accuracy of AVPU, GCS, and RASS for predicting mortality in hospitalized ward patients.

Methods: Nurses at an academic hospital recorded GCS and RASS scores on consecutive adult hospitalizations in the general wards between July 2011 and January 2013. AVPU was extracted from the eye subscale of the GCS. The predictive abilities of AVPU, GCS, RASS, and the subscales of GCS for detecting in-hospital mortality within 24 hours of a mental status observation were compared using areas under the receiver-operator characteristic curves (AUCs).

Results: A total of 295,974 paired observations of GCS and RASS were obtained from 26,873 admissions, of which 417 (1.6%) resulted in in-hospital death. The mean patient age was 57 ±17 years and 23% were surgical patients. GCS and RASS more accurately predicted mortality than AVPU (AUC 0.82 and 0.80, respectively vs. 0.73; P<0.001 for both comparisons). Simultaneous use of GCS and RASS produced an AUC of 0.85 (95% CI: 0.82-0.87; p-value <0.001 when compared to all three scales).

Conclusion: Both GCS and RASS were significantly more accurate predictors of mortality than the more commonly used AVPU scale on the general wards. In addition, the combination of GCS and RASS was more accurate than any scale alone Routine tracking of GCS and RASS in general ward patients may improve the accuracy of detecting clinical deterioration.

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Validating the Use of Visual Analog Scales to Assess Quality of Life and Sleep Quality in Patients with Inflammatory Bowel Disease

Justin Tomal

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**Co-Authors:** Jami Kinnucan, MD; Jonathan H. Stein, MS3; Sarah R. Goeppinger, BA

**Background:** There is great interest in health-related quality of life (HRQoL) among inflammatory bowel disease (IBD) patients, and there is an evolving appreciation for the role sleep and sleep quality play in IBD.[1] In addition, an emerging area of importance by clinicians and regulatory agencies is the use of validated patient-reported outcomes (PROs). In this study of IBD patients, we sought to validate the use of visual analog scales (VAS) by assessing HRQoL as measured by the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) and by assessing sleep quality using the Pittsburgh Sleep Quality Index (PSQI).

**Methods:** We recruited adult patients with a diagnosis of IBD from the outpatient clinic, procedure unit, or inpatient ward at the University of Chicago Medicine. Each patient completed a survey consisting of the following tools: SIBDQ, PSQI and two VAS. The SIBDQ is a validated ten-question survey measuring physical, social and emotional status, with scores ranging from 10 (poor HRQoL) to 70 (good HRQoL).[2] The PSQI is a self-rated questionnaire used to assess sleep quality and disturbances with scores ranging from 0 (good sleep quality) to 21 (poor sleep quality).[3] The VAS were standard 100 mm horizontal lines that represented overall health (SIBDQ) and sleep quality (PSQI), and patients were asked to mark on the line their current state. We measured the distance in mm along the horizontal line to quantify these responses. Statistics included Pearson’s correlation coefficients to compare the SIBDQ, PSQI, and corresponding VAS and Fisher’s exact test to compare sleep quality in patients with active vs. inactive disease.

**Results:** Three hundred patients completed the survey: 158 (53%) females, 189 (63%) patients with Crohn’s disease and 265 (88%) Caucasians. The mean age was 40.8 years (SD 15.8y), while 88 (29%) smoked cigarettes, 43 (14%) had depression, and 43 (14%) had anxiety. The mean SIBDQ score was 50.8 (SD 13.4). The mean PSQI score was 6.9 (SD 4.2), and 55% of patients reported poor sleep quality. There was excellent correlation for the SIBDQ and overall health VAS (r=-.77) and excellent correlation for the PSQI and sleep quality VAS (r=0.73). Additionally, 75.9% of patients with active disease had poor sleep quality compared to 48.6% of patients with inactive disease (P<.0001).

**Conclusion:** In this cross-sectional study, we have demonstrated excellent correlation between the SIBDQ and a simple VAS, and excellent correlation between the PSQI and a simple VAS. Also, our data showed a strong association between disease state and sleep quality in IBD patients. Additional validation studies are underway, but these results support the ongoing use of such instruments in clinical practice and in the evolving area of patient-reported outcomes.

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Patient Perceptions of Fecal Microbiota Transplantation for Ulcerative Colitis

Ashley Vachon

Mentor: David Rubin, MD, Department of Medicine, Section of Gastroenterology

Co-Authors: Stacy Kahn, MD; Dylan Rodriguez; Sarah R. Goeppinger, BA; Bonnie Surma, RN; Julia Marks, BS

Background: Fecal microbiota transplantation (FMT), also known as stool transplant, is the delivery of stool from a healthy, pre-screened individual to someone with inflammatory bowel disease. FMT has been gaining increasing recognition among the public and medical community, especially for its use in gastrointestinal conditions. The most convincing data are taken from studies of its use with Clostridium difficile infections where it has yielded persuasive data regarding safety and efficacy. We conducted this study to establish quantitative evidence that patients with IBD are interested in FMT and to explore social and ethical concerns surrounding FMT.

Methods: We conducted a survey consisting of 38 questions about FMT, disease activity, clinical effectiveness, and satisfaction with current treatments. Questions included multiple choice, rank order, and short answer. We recruited adults with ulcerative colitis (UC) from the inflammatory bowel disease outpatient clinics at the University of Chicago. Those who agreed to participate were entered in a random drawing for a $25 gift certificate. Participants were asked to complete the survey in the clinic. Study data were entered into the Research Electronic Data Capture (REDCap) tools.

Results: Ninety five patients were enrolled into the study and completed the survey with a 95% response rate for the questions. Self-reported disease activity were remission in 59%, mild-to-moderate in 36%, and severe in 5%. Current medical management of UC was reported as excellent in 44%, good/satisfactory in 49%, and poor in 7%. 46% of participants were willing to undergo FMT as a treatment for UC, 43% were unsure and only 11% were unwilling. There is a correlation between disease severity and willingness to undergo FMT but even patients in remission were willing to try them (36%). Hospitalized patients were more likely to be willing to undergo FMT than patients who had not been hospitalized before (55% versus 34%, P=0.035). The most important factors that patients took into considering FMT were effectiveness (38%), safety (26%), failure of conventional medications (21%), and physician recommendation (12%). The main concerns that patients had regarding FMT were adequate screening of fecal matter (41%), cleanliness (24%), and potential to worsen UC (18%). Most patients stated that their preferred method of FMT delivery was by a single sedated colonoscopy (77%), followed by daily enemas for 5 days (20%), and single nasogastric tube delivery (3%). About half the patients (46%) preferred their fecal donor to be whomever their doctor recommended while the other half (46%) preferred a family member or spouse.

Conclusion: We found that the majority of patient with UC that we surveyed were interested in FMT as a potential treatment despite reporting satisfactory to excellent management of their disease by their current medications. The profound interest in FMT not only reflects patients’ desire for more “natural” therapies but also speaks to their dissatisfaction with the current available chronic therapies and lack of medical cure. Disease severity and previous hospitalization for UC were associated with interest in FMT. We expected that patients taking medications with unfavorable side effects, such as corticosteroids, or medications with increased risk of serious adverse events such as immunomodulators and biological therapies to be more interested in FMT. We also hypothesized that patients who reported current use of complementary medicine to be more willing to try FMT because of the perception that it is a more “natural” therapy. However, neither use of alternative medicine or side effects of current medications correlated with willingness to try FMT. Proof of safety and effectiveness, and failure in other therapies are key considerations for willingness to try FMT. Patients seem equally willing to accept either family members or whomever their doctor chooses as their fecal donor.

Limitations to this study included recruitment from a single tertiary care center and small sample population of less than 100. The strong interest in FMT warrants the need for more clinical research and education in this topic for its use in UC.

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The Rates, Perceptions, and Willingness of Men who have Sex with Men to Donate Blood

Nathaniel West

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Background: Since 1983 in the United States, any man who has had sex with another man (MSM) at any time since 1977 has been deferred from donating blood for life. Although there has been a push to change the deferral, there is a paucity of information on both the rates of MSM blood donation, willingness of MSMs to donate if the deferral were changed, and self selection among MSM to defer blood donation in order to protect blood donor pool.

Methods: A 15-question survey was given at two lesbian, gay, bisexual, and transgender LGBT festivals in Chicago and New Orleans. Eligibility was based on being born a biologic male, at least 18 years old, and have had oral or anal sex with male since January 1, 1977. Participants were asked about a previous history of blood donation and whether they would be willing to donate were the lifetime deferral changed. Participants were also asked to determine whether it was safe for hypothetical MSMs with varying sexual practices to donate blood and whether they believed that it was safe for them to donate their own blood.

Results: Our study found that 42.0% of all participants had not complied with the deferral policy and have donated blood at least once, with a mean number of donations of 4.84. Additionally, 85.9% of participants would be willing to donate blood if the deferral were changed. Only 2.2% of men who previously donated “disagree” or “strongly disagree” that it is safe to donate their blood compared to 11.1% of men who have never donated (p = 0.0359). Nearly one-third of participants believed that it was safe for men who are sexually active and do not use condoms 100% of the time to donate blood.

Conclusion: This study demonstrated self selection among MSM to defer blood donation due to perception that their donation may be less safe which likely confounds current models estimating risk of transfusion related disease transmissions. At the same time, many MSM did not perceive the high risk of unprotected sex for disease transmission in the blood donation pool, demonstrating the continued importance of clear behavior based deferral policy and blood donation screening. Despite the lifetime deferral, many MSMs have previously donated blood, and many more are willing to donate. Many MSMs perceived risk of sexual behaviors for transfusion related transmission is discordant with current federal deferral policy, as is their donation practices. Given this, along with the safe implementation of temporary deferral policies in other nations, the United States should consider modifying the blood donation deferral policy, education, and implementation for MSMs.

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Cancer, Functional Decline, and the Vulnerable Elders Survey (VES-13) in Older Medicare Beneficiaries

Peter Wroe

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Co-Authors: Arash Naeim, MD, PhD; Lin Fan, PhD; Supriya Mohile, MD, MS

Background: The US population is aging rapidly, cancer is more prevalent among older adults, and older adults account for a large and growing percentage of cancer cases and deaths. The longitudinal association between a cancer history and functional decline has not been determined, nor has the use of the Vulnerable Elders Survey (VES-13) as a screening tool for predicting decline or death in older cancer survivors.

Methods: Using data from the 2003 and 2004 Medicare Current Beneficiary Survey, we compared older adults with and without a cancer history on functional status (Activities and Instrumental Activities of Daily Living, I/ADLs), geriatric syndromes, and vulnerability (VES-13 score 3 or higher) with chi-squared tests of proportion. We used receiver operating characteristic (ROC) curves to assess the ability of the VES-13 survey instrument (VES-13 score 3 or higher) to predict functional decline or death one year after baseline. We defined functional decline as one of the following: a one-year increase of 2 or more functional deficits, one or more functional deficits after one year if zero functional deficits at baseline, or a nursing home admission.

Results: Older Medicare beneficiaries with a cancer history (n=1,210) were significantly more likely than those without a cancer history (n=5,278) to have functional limitations (56.2% vs. 49.3%, p<.001), geriatric syndromes (58.5% vs. 51.6%, p<.001), and vulnerability (52.5% vs. 43.9%, p<.001) at baseline. Cancer history was not significantly associated with one-year functional decline (18.8% vs. 16.8%, p=.115), but it was associated with death (7.24% vs. 4.03%, p<.001). Based on an ROC curve, the standard 3 or higher screening cut-off on the VES-13 performed similarly between the cancer and non-cancer groups in predicting functional decline or death (Cancer: sensitivity = 69%, specificity = 56%; non-cancer: sensitivity = 64%, specificity = 64%).

Conclusion: Disability, geriatric syndromes, and vulnerability are more prevalent in older Medicare beneficiaries with a cancer history than older adults without cancer. VES-13 predicts functional decline and/or death similarly in the cancer and non-cancer groups. The reasons why older cancer survivors have worse prognosis requires further investigation.

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Correlation of Bispectral Index Scores to Memory Formation Following Premedication with Midazolam

Xiwen Zheng

**Mentor:** David Glick, MD, Department of Anesthesia & Critical Care

**Background:** The Bispectral Index (BIS) has been marketed as a tool to help reduce awareness by measuring the patient's level of consciousness as a score from 0 (no brain activity) to 100 (full consciousness). Previous studies exploring intraoperative use have found that, while effective, BIS is not superior to other methods such as end-tidal anesthetic agent concentration for preventing awareness. This study explored potential perioperative use of BIS through investigating correlation between BIS scores and memory formation after preoperative sedation with midazolam.

**Methods:** After IRB approval and informed consent, 166 benzodiazepine naïve adult subjects were enrolled. A BIS Quatro™ Monitor was placed on patients' foreheads, preoperatively. BIS scores were recorded at 5, 3, and 1 minute before administration of midazolam, immediately after administration, at 1 and 3 minutes after midazolam, and during travel from the preoperative area to the OR. Patients were given a word and instructed to remember it at each BIS score recording, except during travel to the OR. A total of 6 words were given, 3 before and 3 after midazolam. Patients were interviewed at 2 hours and 24 hours postoperative to assess recall of the cued words. A word was considered recalled if patients remembered it without prompting at either interview. Memory of travel from the preoperative area to the OR was also assessed.

**Results:** Statistically significant differences were found between the number of recalled words before and after midazolam (2.3 and 0.9, respectively). The average BIS score for recalled words was 96.4 versus 94.3 for unrecalled words, a difference that was again statistically significant. 67% of patients recalled word 3 (the last given pre-midazolam) whereas only 50% recalled word 4 (the first given post-midazolam). There was no statistically significant drop in BIS scores between words 3 and 4. Recall decreased 22% from word 4 to word 5 while BIS scores saw a statistically significant 2.2-point reduction between those two words. 79.9% of patients recalled traveling to the OR, but BIS scores recorded during travel varied widely in both patients with and without recall.

**Conclusion:** These data suggest that BIS score reductions lag behind initial loss of recall. This may partly be explained by the 30 second running averaging technique used by the BIS monitor, although the actual time between readings was 2 minutes. It is also possible that the BIS score does not capture the most immediate effects of benzodiazepines on memory, or that memory loss under mild sedation is initiated by a route different from that which BIS monitors. Additionally, while the decreases in recall rates were large, the drop in BIS scores was relatively small, suggesting that even statistically significant changes in BIS readings may not be clinically relevant. Moreover, a large percentage of patients recalled travel to the OR, but BIS scores varied widely, suggesting that retention of experiential memories involving multiple stimuli may be even harder to correlate to BIS scores.

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