70th Annual

SENIOR

SCIENTIFIC

SESSION

May 18, 2016
70th Annual
Senior Scientific Session

Wednesday, May 18, 2016

Oral Presentations
1:00 PM – 4:00 PM | Biological Sciences Learning Center - Room 115

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

2016 Session Chair
Dr. Susan Cohn, MD
Professor and Director of Clinical Sciences
Acting Chief, Section of Hematology/Oncology
Department of Pediatrics
Dean for Clinical Research

2016 Presentation Judges

Jacqueline Bernard, MD
Department of Neurology

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

Marshall Chin, MD, MPH
Department of Medicine

Harriet de Wit, PhD
Department of Psychiatry and Behavioral Neuroscience

Elbert Huang, MD, MPH
Department of Medicine

R. Stephanie Huang, PhD
Department of Medicine

Scott Hunter, PhD
Department of Psychiatry and Behavioral Neuroscience

Kristen Knutson, PhD
Department of Medicine

Andrea Lo, MD
Department of Surgery

Doriane Miller, MD
Department of Medicine

Mark Musch, PhD
Department of Medicine

Funmi Olopade, MD
Department of Medicine

Sola Olopade, MD, MPH
Department of Medicine

Tipu Puri, MD, PhD
Department of Medicine

Stephen Small, MD
Department of Anesthesia & Critical Care

Larry Thaete, PhD
Department of Obstetrics and Gynecology
NorthShore University HealthSystem
Welcome & Opening Remarks
Biological Sciences Learning Center - Room 115

1:00 PM Holly J. Humphrey, MD
Ralph W. Gerard Professor in Medicine
Dean for Medical Education

Susan Cohn, MD
Professor and Director of Clinical Sciences
Acting Chief, Section of Hematology/Oncology
Department of Pediatrics
Dean for Clinical Research

Oral Presentations
Abstracts on Pages 13-22

1:15 PM Michael Underriner; Mentor: Susan Ksiazek, MD
A Comparison of Preoperative Laser Interferometry, Potential Acuity Meter, and Dilated Pinhole in Estimating Postoperative Visual Acuity in Cataract Patients

1:30 PM Nisha Wadhwa; Mentor: Peter O'Donnell, MD
Physician Prescribing Behaviors Impacted by On-Demand Pharmacogenomic Results Delivery: Evaluating the Implementation of a Genomic Prescribing System

1:45 PM Robin Wagner; Mentor: David Glick, MD, MBA
Relationship of Awake Bispectral Index to Perioperative Memory Formation

2:00 PM Jillian McKee, PhD; Mentor: David J. Freedman, PhD
Neuronal Representations of Novel and Familiar Visual Stimuli in Macaque Inferior Temporal, Perirhinal and Prefrontal Cortices During a Delayed Match-To-Category Task

2:15 PM Marina Sharifi, PhD; Mentor: Kay F. Macleod, PhD
Autophagy Promotes Focal Adhesion Disassembly, Tumor Cell Motility, and Metastasis Through Src-regulated Degradation of Focal Adhesion Protein Paxillin

2:30 PM BREAK

2:45 PM Steven Bhutra; Mentor: R. Stephanie Huang, PhD
Impute Drug Sensitivity in the Cancer Genome Atlas (TCGA) For Precision Medicine

3:00 PM Kirk Cahill; Mentor: Bakhtiar Yamin, MD
Bcl3 in Glioblastoma

3:15 PM Hila Calev; Mentor: Vineet Arora, MD, MAPP
Prevalence of Impaired Memory in Hospitalized Adults and Associations with In-hospital Sleep

3:30 PM Scott Goldberg; Mentor: Niranjan S. Karnik, MD, PhD
Transitioning from Adolescence to Adulthood: A Qualitative Study of Urban Shelter-Based Homeless Youth

3:45 PM Noah G. Schwartz; Mentor: Babak Mokhlesi, MD, MSc
Sleep Disordered Breathing is Highly Prevalent at Altitude and Associated with Cardio-Metabolic Stress
Poster Presentations
4:15 PM - 6:30 PM | Gordon Center for Integrative Science - 3rd Floor Atrium

Abstracts on Pages 25-50

4:15 PM

Rene Bermea       Ethan Jaffee       Talia Shear
Craig Brown       Caroline Kuhn      Garrick Talmage
Noura Choudhury   Allison Louis     Catherine Trippe
Sahitya Denduluri Jose Morales, MS Adam Vohra
Joshua Eassa      Prithvi Murthy    Adam Weiner
Andrew Golden     Akash Parekh      Blake Williams
Mohammed Hussain  Erin Reed, PhD   Kevin Wymer
James Isaacs      Kathryn Scherpelz, PhD Roseanne (Fang) Zhao, PhD

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 Research 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  Susan Cohn, MD
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In order of presentation

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**APPLIED SCHOLARSHIP**

1. Caroline Kuhn; **Mentor: Kevin Hellman, PhD**
   Functional MRI of Uterus: Application to Primary Dysmenorrhea

2. Talia Shear; **Mentor: Vineet Arora, MD, MAPP**
   Sleepless in the Shelter: A Qualitative Analysis of Sleep in a Transitional Shelter for Women

3. Andrew Golden; **Mentor: Keme Carter, MD**
   Results from the First Year of Implementation of CONSULT: Consultation with Novel Methods and Simulation for UME Longitudinal Training

4. Mohammed Hussain; **Mentor: Lewis Shi, MD**
   Analyses of Distribution of 26,287 U.S. Orthopaedic Surgeons Based on Population Density And Per Capita Income

5. James Isaacs; **Mentor: Lisa Vinci, MD, MS**
   Distribution of Costs in a Patient Population Under a Global Budget

6. Adam Vohra; **Mentor: Kirk Spencer, MD**
   Predicting Heart Failure Readmissions Using a Simplified, Actionable Model

7. Adam Weiner; **Mentor: Scott Eggener, MD**
   National Economic Conditions and Patient Insurance Status Predict Prostate Cancer Diagnosis Rates and Management Decisions

**SCIENTIFIC INVESTIGATION IN BASIC SCIENCES**

8. Sahitya Denduluri; **Mentor: Hue Luu, MD**
   Continuous Adductor Canal Blockade after Primary Total Knee Arthroplasty: A Prospective, Randomized Controlled Trial

9. Jose Morales, MS; **Mentor: Nicholas Hatsopoulos, PhD**
   Evidence of Electrophysiological Activity of Motor Cortex Contralateral to Amputated Limb Exhibiting β-Oscillation Attenuation and Providing Command Signals to Centrally-Implanted Brain Machine Interfaces

10. Akash Parekh; **Mentor: Ralph R. Weichselbaum, MD**
    Cancer Therapies Activate RIG-I-like Receptor Pathway Through Endogenous Non-Coding RNAs

11. Erin Reed, PhD; **Mentor: Elizabeth Grove, PhD**
    Associations of FGF8 with the Olfactory Bulb: Lineage Tracing and Specification of Cell Fate
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Presentation Notes
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—including 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. Dr. Jacobson was 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 and scholarship through oral and poster presentations, the legacy of Dr. Jacobson’s commitment to innovation through research continues.
2015-2016 Calvin Fentress Fellowship Recipients

Rene Bermea
Mentor: Dr. Marcus R. Clark, MD

Steven Bhutra
Mentor: Dr. R. Stephanie Huang, PhD

Craig Brown
Mentor: Dr. Michael Ujiki, MD

Ethan Jaffee
Mentor: Dr. Valerie Press, MD, MPH

Caroline Kuhn
Mentor: Dr. Kevin Hellman, PhD

Allison Louis
Mentor: Dr. Valerie Press, MD, MPH

Prithvi Murthy
Mentor: Dr. Mohan Gundeti, MD

Garrick Talmage
Mentor: Dr. Jacqueline Bernard, MD

Adam Vohra
Mentor: Dr. Rupa Mehta Sanghani, MD

Kevin Wymer
Mentors: Dr. Sangtae Park, MD, MPH and Dr. Beth Plunkett MD, MPH

2015-2016 John D. Arnold, MD Scientific Research Prize Recipients

Noura Choudhury
Mentor: Dr. Yusuke Nakamura, MD, PhD

Akash Parekh
Mentor: Dr. Ralph R. Weichselbaum, MD

Adam Weiner
Mentor: Dr. Scott Eggener, MD
2015-2016 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 2015-2016 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:

Dr. Yusuke Nakamura, MD, PhD

Dr. Nakamura, MD, PhD, has been contributing to genomic medicine and also cancer research fields for nearly three decades. He is one of the pioneers in applying genetic variations (VNTR and SNP markers) and whole-genome analysis in medical science in the world. His contribution in the past can be measured by his publication of more than 1,400 articles that have been cited more than 130,000 times by others. His recent work focuses on the molecular characterization of druggable molecular targets including some kinases and methyltransferases that are specifically expressed in cancer cells. Using cancer-specific molecules, he has developed therapeutic cancer vaccines, antibodies, and small-molecule compounds to treat cancer. In addition, he has been leading the research field of personalized medicine and immunopharmacogenomics.

Dr. Nakamura received the John D. Arnold, MD, Mentor Award for his work with fourth year student Noura Choudhury. Dr. Nakamura and Noura worked attentively together on the association of ErbB family molecular alterations with afatinib sensitivity in platinum-refractory metastatic urothelial carcinoma in a phase II trial. Writing about Dr. Nakamura’s consummate mentorship, Noura commented:

Under Dr. Nakamura’s mentorship, I accepted more freely that I could, and would, learn what I needed to as I went, a mindset that will be tremendously useful as I begin post-graduate clinical training. Most importantly, perhaps the most valuable thing Dr. Nakamura has offered me is his firm belief that I have the ability to contribute significantly to the field of my choice. There is nothing more that I could have asked for in a mentor than what I found in Dr. Nakamura.
Dr. Ralph R. Weichselbaum, MD

Dr. Ralph Weichselbaum specializes in the treatment of potentially curative treatment of "oligo" metastasis with radiotherapy, a concept he first described in 1996. Dr. Weichselbaum's research interests include mechanisms of tumor spread and how radiation therapy and immunotherapy can be used to better treat cancer. He is also studying patterns of gene expression in human tumors that confer resistance to radiotherapy and chemotherapy. Dr. Weichselbaum invented a radio-inducible form of gene therapy with both Adeno and Herpes Viruses, which have been in clinical trials. His research has been funded by the National Institutes of Health for more than 35 years. He is also editor of Cancer Medicine, a definitive reference textbook compiled to help oncologists and internists apply scientific principles to clinical practice.

Dr. Weichselbaum received the John D. Arnold, MD, Mentor Award for his work with fourth year student Akash Parekh. In their work together, Dr. Weichselbaum and Akash researched how ionizing radiation activates RIG-I-like receptor pathway through endogenous non-coding RNAs. Akash spoke highly of the impact that Dr. Weichselbaum had on his professional development, writing:

_It was a privilege to work with and receive training from one of the most respected radiation oncologists in the country, especially since I had strong interest in the field. Beyond the science, research required I persevere despite experimental failures and adapt as new results arrived. I learned about effective communication within the scientific community and the tenants of defending my ideas. Dr. Weichselbaum helped me realize that clinical care and research could work in tandem._

Dr. Scott Eggener, MD

Dr. Scott Eggener, MD, is a high-volume robotic and open surgeon who specializes in the care of patients with urologic malignancies. Dr. Eggener's research has resulted in over 175 publications. He serves on the editorial board of four urologic journals, and is an executive board member of IVUMed, the largest urologic international service organization. Dr. Eggener is also a senior faculty scholar at the Bucksbaum Institute for Clinical Excellence.

Dr. Eggener received the John D. Arnold, MD, Mentor Award for his work with fourth year student Adam Weiner. Dr. Eggener and Adam analyzed if national and local economic conditions predict prostate cancer diagnosis rates and management decisions. Commenting on Dr. Eggener's outstanding style of mentorship, Adam noted:

_… research with Dr. Eggener began early during my medical school experience. Quickly, his talent at motivating became apparent. I remember clearly one meeting in which I expressed my concerns after struggling for weeks to understand how to use the statistical software. With adept compassion, he validated my concerns and expressed how he had seen several medical students overcome the learning curve. I left the meeting feeling more confident and equipped to meet the challenge of learning statistics. Dr. Eggener has been consistently available in a timely manner to offer feedback and suggestions and guide me through one obstacle after another, extending well beyond his role as a research principal investigator._
Oral Presentations
A Comparison of Preoperative Laser Interferometry, Potential Acuity Meter, and Dilated Pinhole in Estimating Postoperative Visual Acuity in Cataract Patients

Michael Underriner

**Mentor:** Susan Ksiazek, MD, Department of Ophthalmology & Visual Science

**Co-Authors:** Janice McMahon, OD; Susan Ksiazek, MD

**Background:** More than three million individuals in the U.S. undergo lens replacement for cataracts each year. The success rate, defined as best corrected visual acuity (BCVA) greater than 20/40, exceeds 90%. Macular problems are the most prevalent contributor to postoperative dissatisfaction. Several methods are available to predict postoperative BCVA and minimize the likelihood of performing unsuccessful surgery in patients with macular comorbidity. Laser interferometry (LI) projects an image on the retina that the patient then deciphers. Potential acuity meter (PAM) uses white light through a pinhole aperture to project the Snellen acuity chart on the retina. Dilated pinhole examination (PH) consists of asking the patient to read a near card at 14 inches through a 0.3 mm pinhole in a bright room. No study has directly compared all three measurements. We aim to assess PAM, LI, and PH as screening tests, calculating their sensitivity, specificity, and positive and negative predictive values in predicting successful cataract surgery. We also aim to plot the linear correlation between postoperative BCVA and predicted BCVA for each metric.

**Methods:** This study was conducted as a prospective case series. Patients were enrolled consecutively at Dr. Ksiazek's clinic at the Illinois College of Optometry (ICO). Each patient participated in three visits, in addition to the surgery. All three measures of BCVA were collected at ICO or UCMC by trained staff. At the one-month postoperative appointment, BCVA was assessed using a standard Snellen acuity chart. Sensitivity, specificity, and positive and negative predictive values were calculated for each preoperative assessment, using a BCVA of 20/40 as indicative of a successful surgery.

**Results:** 192 consecutive patients at ICO were offered enrollment in the study over the course of 18 months. A total of 84 patients agreed to participate, underwent surgery, and attended the one-month follow-up appointment. None of the three measures had a strong linear correlation with postoperative BCVA. The coefficient between PH and postoperative BCVA was highest at 0.38, significantly stronger than for either PAM or LI. The specificity of PAM (84.2%) was higher than either LI (63.2%) or PH (78.9%), but not significantly so. The sensitivity of all three measurements was lower than 60%.

**Conclusion:** Preoperative measurements of postoperative BCVA do not reliably identify the subset of patients unlikely to benefit from cataract extraction. However, these techniques may discern which patients will undergo successful surgery. PH had the highest linear correlation with postoperative BCVA and was not statistically worse than PAM in terms of sensitivity, specificity, PPV, or NPV. Given that it requires no proprietary equipment to conduct a pinhole examination, this constitutes the most reasonable choice for clinicians prior to performing cataract surgery.

**Acknowledgements/Disclosures:** Shirley Rodriguez, Department of Surgery, UCMC; Maryana Petrovic and Patrycja Grudzinka, Department of Ophthalmology & Visual Science, UCMC
Physician Prescribing Behaviors Impacted by On-Demand Pharmacogenomic Results Delivery: Evaluating the Implementation of a Genomic Prescribing System

Nisha Wadhwa

**Mentor:** Peter O'Donnell, MD, Department of Medicine, Section of Hematology/Oncology

**Co-Authors:** Keith Danahey, MS, MSc; Sang Mee Lee, PhD; Julienne Faust, BS; Sheena Hussain, BS; Catherine Klammer, BS; Brittany Borden, BS; Linda Patrick-Miller, PhD; Mark Siegler, MD; Matthew J. Sorrentino, MD; Andrew Davis, MD; Yasmin Sacro, MD; Walter Stadler, MD; Rita Nanda, MD; Tamar Polonsky, MD; Jay Koyner, MD; Edward K Leung, PhD; Jerry Yeo, PhD; David Meltzer, MD, PhD; Russ B Altman, MD; Olufunmilayo I. Olopade, MD; Mark J Ratain, MD; Peter O'Donnell, MD

**Background:** Determining feasible methods for delivery of results is a significant barrier to pharmacogenomic (PGx) implementation. We hypothesized that PGx results delivered via a physician (MD) portal would significantly influence prescribing decisions.

**Methods:** This study evaluated the use of an MD-accessible web portal called the Genomic Prescribing System (GPS), which provides MDs with patient-specific PGx results categorized as green (favorable), yellow (cautionary), and red (high risk) alerts. To characterize prescribing behaviors, MD-user GPS click logs for outpatient visits from October 2012 to September 2015 were analyzed in conjunction with electronic medical records.

**Results:** A total of 2279 patient encounters across eight specialties at which PGx results were accessible were analyzed, with a total of 801 medication changes made during this time. At 70% of visits, study MDs accessed GPS, corresponding to 2869 PGx alerts being delivered on drugs patients were already taking. Likelihood of medication changes in drugs with alerts corresponded to alert severity, with OR of 26.15 (9.08-75.25, p<0.0001) for red and 2.4 (1.65-3.5, p<0.0001) for yellow. Green-light medications were changed at the same rate as drugs without PGx information. Among medication changes in drugs with PGx information available, 53% of new medications, 68% of discontinued medications, and 50% of dose changes were influenced by GPS. A total of 412 red and yellow alerts were not delivered.

**Conclusion:** Our analysis of physician behaviors surrounding PGx suggests that the results delivered significantly impacted physician prescribing behaviors in a pattern that was consistent with the degree of risk conveyed by the PGx alerts, demonstrating that physicians were able to incorporate this model of PGx delivery into routine clinical care. High risk PGx results did not consistently result in prescription changes, indicating that advanced decision support and ongoing refinement of PGx delivery may be necessary.

**Acknowledgements/Disclosures:** P.H.O., K.D., and M.J.R. are coinventors of a pending patent application for the Genomic Prescribing System. M.J.R. is a coinventor holding patents related to pharmacogenetic diagnostics and receives royalties related to UGT1A1 genotyping. No royalties were received from the genotyping performed in this study. This research was supported by the following grants: The University of Chicago Pritzker Summer Research Program (N.R.W), NIH K23 GM 100288-01A1 (P.H.O.), The Conquer Cancer Foundation of the American Society for Clinical Oncology (M.J.R.), The Central Society for Clinical and Translational Research, Early Career Development Award (P.H.O.), NIH/National Heart, Lung, and Blood Institute grant 5 U01 HL105198-09 (M.J.R. and P.H.O.), and The William F. O'Connor Foundation (M.J.R.)
**Relationship of Awake Bispectral Index to Perioperative Memory Formation**

Robin Wagner

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

**Co-Authors:** Katherine Palmer, BA; Dan Alexander, BA, MPP; Daniel Blech, BA; Patrick O'Connor; Michael F O'Connor, MD; David Glick, MD, MBA

**Background:** Anesthesia awareness is a rare but significant complication of general anesthesia. As such, "awareness" monitors have been developed to target to the appropriate depth of anesthesia. One such monitor, the Bispectral Index (BIS) (Covidien) uses an algorithmically processed EEG and EMG to output a dimensionless integer ranging from 0 (electrical silence) to 98 (complete wakefulness). Initial studies indicated that BIS improved upon other anesthetic monitoring techniques in preventing awareness. Subsequent studies have indicated that BIS is no better or worse than control protocols. This study was designed to characterize whether BIS is related to a subject's memory formation, a prerequisite for reporting awareness events, by assessing recall of words spoken in the perioperative setting.

**Methods:** Following IRB approval and informed consent, 308 adult subjects undergoing procedures involving administration of general anesthesia were enrolled. Preoperatively, BIS values were recorded at five, three, and one minute prior to midazolam administration; at the time of administration; and at one, three and five minutes post-administration. At the first six time points, a unique word was spoken and the subject was asked to remember the word. Postoperatively, six additional unique words, each repeated seven times, were spoken at 20-minute intervals, with BIS values recorded at each repetition. Word recall was assessed post-operatively and at 24 hours, and relationship of BIS to recall was analyzed using logistic regressions. The relationship of duration of anesthesia to recall was also examined.

**Results:** Logistic regressions of recall on BIS values for the preoperative words spoken prior to midazolam administration revealed no statistically significant relationship. For preoperative words spoken after midazolam administration, the odds ratio of recall was 2.77 (95% CI 1.78–4.30) for each standard-deviation (6 point) increase in BIS. A statistically significant (p<0.05) decline in recall of words was observed starting one minute prior to midazolam administration. For words spoken in the postoperative period, the odds ratio of recall was 1.639 (95% CI 1.256–2.138) for each standard-deviation (6 point) increase in BIS. None of these results changed substantively (in sign, statistical significance, or clinical significance) when controlling for covariates or including random effects. The relationship between recall and duration of anesthesia was not significant for preoperative words. For postoperative words, the odds ratio for recalling words was 0.717 (95% CI 0.589–0.874) for each one-hour increase in anesthetic duration.

**Conclusion:** BIS value emerges as a predictor of recall in the perioperative setting following administration of midazolam or general anesthetic agents, even accounting for its correlation with other subject attributes. Additionally, duration of anesthesia appears negatively correlated to postoperative memory formation. These findings constitute the first evidence that BIS reflects memory in the perioperative setting and offer insight into the retention of information by patients perioperatively.

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Neuronal Representations of Novel and Familiar Visual Stimuli in Macaque Inferior Temporal, Perirhinal and Prefrontal Cortices During a Delayed Match-To-Category Task

Jillian McKee, PhD

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**Co-Authors:** Stephanie L. Thomas, MBA; David J. Freedman, PhD

**Background:** Humans have a remarkable ability to quickly recognize whether a visual stimulus is novel or familiar. This skill is of great behavioral importance, as it allows us to rapidly identify new or changing aspects of our environment. Previous studies have demonstrated that the activity of neurons in prefrontal (PFC), perirhinal (PrC) and inferior temporal (ITC) cortices can differentiate between novel and familiar stimuli. However, the relationship between neuronal familiarity effects and perception/behavior is not well understood.

**Methods:** Two adult male rhesus macaques were trained to perform a delayed match-to-category (DMC) task where visual stimuli were matched based on their level of familiarity, with familiar images being match to other familiar images and novel images being matched to other novel images. Each animal was implanted with two recording chambers to provide access to PFC and ITC/PrC, through which single-unit extracellular recordings were obtained from up to 20 electrodes per recording session. We recorded from neurons in ITC (N=211), PrC (N=210) and PFC (N=440) while the monkeys performed the DMC task. Neuronal activity to novel and familiar images was examined at both the single unit and population levels. Due to variability in neuronal response patterns, we took a population decoding approach to determine what information could be extracted from each area during different task epochs. Support vector machine (SVM) based classifiers were designed to distinguish between stimuli (which image) or categories (novel or familiar) in different task epochs, using pseudopopulations of neurons (i.e. neurons recorded during different sessions were combined).

**Results:** Single neurons displayed a variety of responses, with some having strong selectivity for either novel or familiar stimuli while others had increased activity to a particular image. The population decoding analyses revealed strong category and feature encoding in ITC and PrC, while PFC neurons showed stronger novel/familiar selectivity and weaker feature encoding. During the decision/response period of the task, when subjects are comparing sample and test stimuli and deciding if they belong to same or different categories, we could decode the category of the currently visible stimulus in all 3 areas, but with lower accuracy in PFC. When decoding the category of the stimulus held in memory and whether it was a match or nonmatch trial, neurons in PFC outperformed those in ITC and PrC in both cases.

**Conclusion:** Together, our results suggest that temporal cortex is involved in both visual feature representation and categorization, while frontal cortex encodes abstract category information, maintains this information into the decision period to facilitate decision making, and encodes information pertaining to the behavioral output of the task.

**Acknowledgements/Disclosures:** NSERC-PGSD, NSF CAREER Award, Alfred P. Sloan Foundation, and The McKnight Endowment Fund for Neuroscience.
Autophagy Promotes Focal Adhesion Disassembly, Tumor Cell Motility, and Metastasis Through Src-Regulated Degradation of Focal Adhesion Protein Paxillin

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Background: Macro-autophagy is a catabolic process important for the degradation of damaged organelles as well as the intracellular recycling of metabolites that are used by tumor cells to survive nutrient stress, hypoxia and cytotoxic therapies (Kimmelman, 2011). Consequently, autophagy has emerged as a potential therapeutic target (Amaravadi et al., 2011). Increased staining for the autophagy marker LC3 has been associated with node positivity in human breast cancer, while melanoma metastases have increased LC3 staining compared to matched primary tumors (Lazova et al., 2012), However, whether autophagy directly contributes to the metastatic cascade is not well understood.

Methods: To examine the role of autophagy in metastasis, we utilized the 4T1 mammary tumor model, in which 4T1 murine mammary carcinoma cells implanted into the mammary fat pad of syngeneic mice form primary tumors that metastasize to the lung and liver. We inhibited autophagy in 4T1 cells both chemically and through shRNA-mediated knockdown of Atg5 or Atg7, two essential autophagy proteins.

Results: Inhibition of autophagy in 4T1 cells markedly reduced metastasis to the lungs and liver without affecting primary tumor growth. However, autophagy deficient cells colonized the lungs to the same extent as control cells when introduced directly into the circulation via tail vein injection, suggesting that inhibition of autophagy impairs escape from the primary tumor. Indeed, inhibition of autophagy inhibited cell migration and invasion through collagen in 4T1 cells, MDA-MB-231 human breast cancer cells, and B16.F10 melanoma cells. This is associated with impaired focal adhesion disassembly and accumulation of the key focal adhesion component paxillin. We showed that siRNA knockdown of paxillin in autophagy-deficient cells rescues their motility, suggesting that impaired focal adhesion disassembly and migration in autophagy-deficient cells is caused by failure of autophagic degradation of paxillin. We demonstrate that paxillin is targeted for autophagic degradation via direct interaction with core autophagosome component LC3, and that this interaction occurs through a conserved LIR (LC3 interacting region) in paxillin. Finally, we show that this interaction is regulated by SRC phosphorylation of paxillin, and is required for stimulation of tumor cell motility by oncogenic SRC.

Conclusion: We have demonstrated that autophagy promotes migration and invasion of metastatic tumor cells in vitro and is required for metastasis in the 4T1 mammary tumor model in vivo. We show that autophagy promotes the degradation of paxillin and focal adhesion turnover via a direct interaction between autophagosome protein LC3 and paxillin. Finally, we show that this interaction is regulated by SRC and is required for SRC-driven tumor cell motility. This work identifies a novel and unexpected function for autophagy in tumor cell motility and metastasis that suggests the possibility of targeting autophagy to inhibit metastatic dissemination therapeutically.

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Impute Drug Sensitivity in the Cancer Genome Atlas (TCGA) for Precision Medicine

Steven Bhutra

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Background: Exemplified by Hoadley et al.’s publication, high throughput molecular profiling has enabled the reclassification of cancers into novel molecular subtypes beyond simply tissue of origin. However, actionable therapeutic strategy based on these newly defined molecular cancer types remain under studied. Thus the results of the 20 comprehensive molecular analysis to date within the Cancer Genome Atlas (TCGA) have led to minimal changes to the standard of care in cancers. Here, in an effort to select the optimal treatment agents given a defined molecular background for cancer, we propose to apply a newly developed powerful drug sensitivity prediction method to TCGA. Our goal is to decipher optimal drug/molecular profile relationship and use that to tailor therapy.

Methods: A diverse panel of about 700 cancer cell lines from Cancer Genome Project were used to build models relating gene expression to drug response generated from a high-throughput drug screen of over 130 drugs. These models were applied to gene expression data in TCGA, a study containing gene expression (RNA-seq) data from tumors of over 10,000 cancer patients. This yields an imputed drug sensitivity value for over 130 drugs for each tumor sample in TCGA. The imputed drug sensitivity is then compared within and among different molecularly defined subtypes with the goal of identifying optimal therapy for each disease subtypes. In particular, we looked into optimizing treatment of the heterogeneous subtypes of bladder cancer by focusing on samples with predicted resistance to standard of care as well as sensitivity to novel therapies already in clinical trials.

Results: Initially we analyzed two previously well documented clinically efficacious targetable drugs: lapatanib and erlotinib. Consistent with prior evidence, our model predicts lapatinib to be more sensitive in the HER2+ compared to HER2- breast cancer samples (p < 0.01) and erlotinib to be more sensitive in EGFR mutant compared to non-mutant lung adenocarcinoma samples (p < 0.01). A previous pan-TCGA analysis have divided bladder cancer into three molecularly-distinct subtypes: LUAD-like, squamous and bladder. When focusing on the bladder subtype, we found patients with imputed resistant to standard-of-care agents had a worse prognosis than patients with sensitive predictions. Interestingly, for those TCGA bladder subtype samples that predicted to be resistant to the standard of care, our method predicted that they would respond well to two targeted agents, pazopanib and temsirolimus, both of which are being evaluated by ongoing clinical trials. In addition, we identified several other novel therapies including a Rac GTPase inhibitor and tyrosine kinase inhibitor in these resistant setting.

Conclusion: We generated imputed drug sensitivity for a large collection of tumor samples available through TCGA based on their transcriptome profile. These data provide promising tools for future studies aimed at tailoring therapy and drug repurposing.

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Bcl3 in Glioblastoma

Kirk Cahill

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Background: Despite multi-modal therapy including surgery, radiation, and temozolomide (TMZ), resistance to treatment is nearly universal in patients with glioblastoma. The nuclear factor-kB (NF-kB) pathway plays an important role in promoting resistance to therapy. Mutations and copy number aberrations in NF-kB transcription factor subunits are rare, suggesting co-regulators may contribute to treatment resistance. We hypothesized that the NF-kB co-regulator, Bcl3, modulates NF-kB gene transcription in the cytotoxic response to TMZ and promotes glioma cell survival.

Methods: Glioblastoma cells were grown in DMEM (enriched with FBS, penicillin, and streptomycin) at 37°C and 5% CO2. Si-control and si-Bcl3 were transfected with oligofectamine. Sh-control and sh-Bcl3 oligos were cloned into lentivirus pLKO.1-puro plasmid. For overexpression, human Bcl3 sequence was cloned into lentivirus pLVX-puro plasmid. After infection, cells were selected with puromycin. Whole cell lysates were subjected to SDS-PAGE and western blotted using antibodies to Bcl3 and GAPDH. Clonogenic assays were treated with TMZ 24 hrs after plating, and colonies counted 10 days later. Trypan blue cell death assays were counted 72 hrs post-treatment with TMZ. IRB approved glioblastoma tissue specimens were stained using anti-Bcl3 and graded in blinded fashion with a four-tier system converted into a binary scale. Gene expression data was obtained from The Cancer Genome Atlas (TCGA). Kaplan Meier curves were generated using Stata and compared with log-rank tests. Multivariate analysis using Cox regression included gene expression, age, Karnofsky score, sex, and treatment. All other results expressed as mean ±SD and significance determined as a p <0.05 using a two-tailed Student t test.

Results: Experiments in glioma cell lines demonstrate that loss of Bcl3 increases the sensitivity to TMZ, while overexpression increases survival in response to TMZ but not at baseline. Expression data from TCGA of over 500 patients with glioblastoma demonstrates that Bcl3 mRNA level is an independent prognostic factor for overall survival on multivariate analysis. Patients with high Bcl3 mRNA expression have significantly poorer survival. On further analysis, patients treated with TMZ are separated into survival groups, with high Bcl3 doing poorly. In untreated patients, no survival difference is seen suggesting that Bcl3 is not prognostic, but rather predictive of treatment response. Additionally, Bcl3 immunostaining in glioma tissue specimens separates patients into good and bad survival groups with high Bcl3 doing poorly.

Conclusion: We identify Bcl3 as a novel biomarker in glioblastoma that predicts response to TMZ treatment. Targeting Bcl3 may enhance the anti-glioma effect in patients who respond poorly to standard treatment. Future experiments include examining Bcl3-dependent gene expression to identify potential downstream targets.

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Prevalence of Impaired Memory in Hospitalized Adults and Associations with In-Hospital Sleep

Hila Calev

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**Co-Authors:** Lisa M. Spampinato, BS; Valerie Press MD, MPH; David O. Meltzer MD, PhD; Vineet Arora MD, MAPP

**Background:** Effective inpatient teaching requires intact patient memory, but studies suggest hospitalized adults may have memory deficits. Sleep loss among inpatients could contribute to memory impairment.

**Methods:** Prospective cohort study designed to assess memory in older hospitalized adults, and to test the association of memory with sleep quantity, sleep quality, and subjective sleepiness, in order to identify a possible contributor to memory deficits in these patients. Subjects were 107 hospitalized adults on the general medicine and hematology/oncology inpatient wards who were at least 50 years of age with no diagnosed sleep disorder. Immediate memory and memory after a 24-hour delay were assessed using a word recall and word recognition task from the University of Southern California Repeatable Episodic Memory Test (USC-REMT). Subjective sleepiness was assessed using the Epworth Sleepiness Scale and a modified Functional Outcomes of Sleep Questionnaire. A vignette-based memory task was piloted in a subset of patients as an alternative test more closely resembling discharge instructions. Sleep duration and sleep efficiency overnight in the hospital were measured using actigraphy.

**Results:** Mean immediate recall was 3.9 words out of 15 (SD=2.1). Forty-seven percent of subjects had poor memory, defined as immediate recall score of 3 words or lower. Median immediate recognition was 11 words out of 15 (IQR=9, 12). Median delayed recall score was 1 word and median delayed recognition was 10 words (IQR= 8-12). Older age and male sex were significantly associated with worse memory performance (p<0.05). There was no association of memory performance with nighttime sleep, daytime sleep or subjective sleepiness. This held even when controlling for self-reported Charlson Comorbidity Index. The medical vignette task was completed in a subset of 36 subjects. The medical vignette memory score was significantly correlated with immediate recall score (r=0.48, p<0.01).

**Conclusion:** About half of inpatients studied had poor memory while in the hospital, signaling that hospitalization might not be an ideal teachable moment. In-hospital sleep was not associated with memory scores.

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Transitioning from Adolescence to Adulthood: A Qualitative Study of Urban Shelter-Based Homeless Youth

Scott Goldberg

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Co-Authors: Scott Hunter, PhD; Niranjan S. Karnik, MD, PhD

Background: On any given night in the United States, there are about 1.7 million homeless youth. Youth homelessness is associated with many adverse outcomes including poorer cognitive functioning, academic performance, and physical and mental health. There is a dearth of research focused specifically on homeless youth between the ages of 18 and 24, a population of special interest because of the critical aspects of this developmental period. Even less is known about young adults living in shelters, who represent an important sub-population because they have greater access to resources and social services than do their street-based counterparts. This qualitative study explores the question of – once housing status is controlled for – what characteristics do individuals possess whom are effectively utilizing shelter resources to navigate the important transition to early adulthood.

Methods: Ten shelter-based youth completed demographic surveys, IQ tests, and semi-structured individual interviews. The data from the interviews was analyzed using standard qualitative methods. A thematic framework was developed and informative quotes were sorted under relevant themes. Individuals were split into two groups and compared based on their enrollment in higher education.

Results: Students in school experienced less homeless episodes in the past year than their non-enrolled counterparts. They also had statistically significant higher scores on the WASI Performance IQ and Full-Scale IQ assessments. The qualitative responses demonstrated that students in school were more likely to report: concrete and realistic goals, resilience in the face of challenging circumstances, and access to helpful social support. Participants not in school were more likely to report: unrealistic life goals, difficulty with emotional and behavioral control, and a lack of or unwillingness to access social support.

Conclusion: This study demonstrates that long-term stable housing and resources are critical for homeless youth development. It also provides insights, both quantitative and qualitative, into why some shelter-based homeless adolescents are more successful than their peers at navigating the transition to adulthood, as defined by enrollment in college. These insights can form a framework for interventions and policies that seek to identify homeless adolescents that require additional support and assistance during this critical life stage.

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Sleep Disordered Breathing is Highly Prevalent at Altitude and Associated With Cardio-Metabolic Stress

Noah G. Schwartz

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Background: Sleep disordered breathing (SDB) is a highly prevalent condition that has been increasingly recognized as a potent cause of cardiovascular morbidity and mortality. Acute exposure to high altitude has been shown to worsen SDB severity, but the effects of chronic exposure have not been well characterized.

Methods: To investigate the prevalence and severity of SDB at high altitude, we recruited a convenience sample of 206 participants from a population-based representative cohort of 1,476 adults residing in Puno, Peru at 3,825 meters above sea level. Participants underwent a single night of home-based physiologic recordings including respiratory effort, airflow, pulse-oximetry, and actigraphy. SDB was characterized by the frequency of apneas and hypopneas per hour (Apnea-Hypopnea Index, AHI); the types of apneas/hypopneas (obstructive, central, mixed); and oxyhemoglobin saturation (SpO₂) during sleep versus wakefulness. Multivariable linear regression models were constructed to investigate cross-sectional associations between SDB severity and biomarkers of cardio-metabolic stress, adjusting for age, sex, and BMI. SDB metrics included log AHI and mean nocturnal SpO₂. Stress biomarkers included systolic blood pressure and measures of glucose intolerance (hemoglobin A1c) and chronic mountain sickness (hemoglobin).

Results: The study sample consisted of 105 men and 101 women, with a mean age of 55.6 ± 12 years and mean body mass index (BMI) of 26.9 ± 4.1 kg/m². The prevalence of SDB was strikingly high at each conventional level of severity: 78.2% of participants had mild to severe SDB (AHI ≥ 5), 37.4% had moderate to severe SDB (AHI ≥ 15), and 16.8% had severe SDB (AHI ≥ 30). On average, 56.1% of SDB events were obstructive, 41.6% central, and 1.6% mixed. Participants experienced marked desaturation during sleep, with a mean sleep SpO₂ of 82.6 ± 2.6%, compared to a mean wake SpO₂ of 86.3 ± 2.2%. SDB events were associated with severe desaturations, with a mean low SpO₂ during SDB events of 79.3% ± 3.3%. In multivariable linear regressions adjusting for age, sex, and BMI, log AHI was significantly associated with elevated hemoglobin A1c (p = 0.02); and low nocturnal SpO₂ was significantly associated with elevated hemoglobin A1c (p < 0.001) and elevated hemoglobin (p = 0.02).

Conclusion: Sleep disordered breathing is highly prevalent in Peruvian highlanders and associated with severe hypoxemia and biomarkers of cardio-metabolic stress. These findings suggest a pressing need to develop feasible, scalable SDB treatments for high-altitude populations worldwide to reduce cardiovascular sequelae.

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Applied Scholarship
**Functional MRI of uterus: Application to primary dysmenorrhea**

Caroline Kuhn

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**Co-Authors:** Nathan Shlobin; Potthumarthi Prasad, PhD; Kevin Hellman, PhD

**Background:** The mechanisms responsible for menstrual pain are poorly understood but are thought to involve uterine contractions, vascular resistance, and ischemia. Therefore, we sought to establish the relationship between menstrual cramps and uterine oxygenation with the use of blood oxygen level-dependent (BOLD) and half-fourier acquisition single-shot turbo spin-echo (HASTE) MR imaging.

**Methods:** Subjects were instructed to continuously report pain using a squeeze bulb on both a menses and non-menses day. Sagittal HASTE MRI was performed while simultaneously recording bulb squeezes. BOLD videos were acquired in a Siemenes Magnetom Verio 3T scanner to measure uterine oxygenation. Subjects were given 440 mg sodium naproxen to alleviate menstrual pain, and underwent repeat episodes of scanning. Subjects were then given supplemental oxygen at 10 liters/minute for 2 minutes. HASTE and BOLD sequences were analyzed offline by a pair of blinded reviewers.

**Results:** BOLD signal increased on average 3.6 ± 0.6 % after O₂ supplementation (p<0.05) with the administration of supplemental O₂. Transient reductions of 5% signal lasting 20 seconds or longer were characteristics uniquely associated with dysmenorrhea participants during their menses. Nine out of 12 women with menstrual pain during their menses had these repetitive episodes of transient reductions in BOLD signal intensity. In contrast, only 2 out of 11 of these women had episodes of transient reductions during their non-menses visits. None of the healthy controls had episodes of transient reduction in BOLD signal intensity. After NSAIDS, only 4 menstrual pain subjects continued to have transient BOLD signal reductions greater than 5%. Notably, 2 of these 4 women that did not have reduced BOLD activity also continued to have significant levels of pain after NSAIDS.

**Conclusion:** Our results imply that BOLD and HASTE MRI can be used to evaluate the role of uterine ischemia in dysmenorrhea. This may further facilitate the development of therapeutics that may treat menstrual pain.

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Sleepless in the Shelter: A Qualitative Analysis of Sleep in a Transitional Shelter for Women

Talia Shear

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Background: Shelters are intended to offer refuge, security, and opportunities for healing. However, despite the invaluable services they provide, shelters may not always provide the peace and quiet needed for restorative functions, such as sleep.

Sleep disturbances among sheltered populations and their functional impact remain largely unstudied. Although both personal variables such as intimate partner violence (IPV) have been found to significantly affect sleep, no known studies have specifically investigated environmental variables, such as noise and perceived physical security, and attempted to solicit ideas for improvement from shelter residents themselves.

Methods: The study was conducted at a transitional shelter for women and children in Chicago. Female residents aged 18 and older and not pregnant at the time were eligible for the study. Following consent to participate in the study, subjects were interviewed and recorded using a structured interview guide to elicit perceptions regarding sleep disturbances in the shelter. For qualitative interview data acquired, transcripts were reviewed and analyzed using the constant comparative method based in grounded theory. An inductive approach was used to develop a coding scheme after review of an initial small transcript sample. The coding scheme was then applied to the entire set of transcripts by the investigators.

Results: 22 shelter residents consented to and participated in the study. Major themes that emerged as sleep disruptors were as follows: (a) Built environment, including lighting and dorm room set-up of sleeping quarters; "[Sleep is] very short, very interrupted...people have different rituals, or whatever for going to sleep, and I’m not used to that, and it's eleven in our room." (b) Social environment, including poor rule compliance and/or enforcement; "Instead of going out in the hall where they're supposed to and talk on the phone, [they] just lay there and get to talking, or the alarms of the cellphones [disturb sleep]." (c) Perceived security concerns for self and/or belongings; "It's hard to go to sleep, because...you can't have nothing really on lockdown, so you got to worry about people stealing, because that's always happening." and (d) Stress; "And now, I'm stressed again, because I didn't plan on being here this long... so, no, sleep is not good at all."

The majority of residents (12/22, 54.5%) reported daytime sleepiness, ranging from mild to significant. The majority of residents (17/22, 77.3%) also reported that they believed sleep was important to health. Consistent rule enforcement by staff, reducing number of roommates, promoting respect/courteous behavior between residents, and locking up items to reduce security concerns were commonly identified by residents as means by which to improve sleep in the shelter.

Conclusion: Several external disruptions to sleep in the shelter are present and may impact daily mood and functioning. Many of these identified disruptions are modifiable, providing the opportunity for future intervention.

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Results from the First Year of Implementation of CONSULT: Consultation with Novel Methods and Simulation for UME Longitudinal Training

Andrew Golden

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Background: An important area of communication in healthcare is the consultation. Existing literature suggests that formal training in consultation communication is lacking. We aimed to conduct a targeted needs assessment of third-year students on their experience calling consultations, and based on these results, develop, pilot, and evaluate the effectiveness of a consultation curriculum for different learner levels that can be implemented as a longitudinal curriculum.

Methods: Baseline needs assessment data were gathered using a survey completed by third-year students at the conclusion of the clinical clerkships. The survey assessed students' knowledge of the standardized consultation, experience and comfort calling consultations, and previous instruction received on consultation communication. Implementation of the consultation curriculum began the following academic year. Second-year students were introduced to Kessler's 5 Cs consultation model through a didactic session consisting of a lecture, viewing of "trigger" videos illustrating standardized and informal consultations, followed by reflection and discussion. Curriculum effectiveness was assessed through pre- and post- curriculum surveys that assessed knowledge of and comfort with the consultation process. Fourth-year students participated in a consultation curriculum that provided instruction on the 5 Cs model and allowed for continued practice of consultation skills through simulation during the Emergency Medicine clerkship. Proficiency in consult communication in this cohort was assessed using two assessment tools, the Global Rating Scale and the 5 Cs Checklist.

Results: The targeted needs assessment of third-year students indicated that 93% of students have called a consultation during their clerkships, but only 24% received feedback. Post-curriculum, second-year students identified more components of the 5 Cs model (4.04 vs. 4.81, p<0.001) and reported greater comfort with the consultation process (0% vs. 69%, p<0.001). Post-curriculum, fourth-year students scored higher in all criteria measuring consultation effectiveness (p<0.001 for all) and included more necessary items in simulated consultations (62% vs. 77%, p<0.001).

Conclusion: While third-year medical students reported calling consultations, few felt comfortable and formal training was lacking. A curriculum in consult communication for different levels of learners can improve knowledge and comfort prior to clinical clerkships and improve consultation skills prior to residency training.

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Analyses of Distribution of 26,287 U.S. Orthopaedic Surgeons Based on Population Density and Per Capita Income

Mohammed Hussain

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Co-Authors: Haroon Hussain MD; Waqas Hussain MD; Hristo Piponov; J.M. Leland III, MD; Douglas Dirschl, MD; Lewis Shi, MD

Background: With a rising and an aging population, it is imperative to meet the growing need for orthopaedic care in the United States. There are personal and societal factors that affect the geographic distribution of orthopaedic surgeons. We analyze the distribution of all US active orthopaedic surgeons based on population density and per capita income, in an attempt to answer whether surgeon supply is meeting patient demand.

Methods: A directory of 26,287 active U.S. orthopaedic surgeons was studied that included name, mailing address, county, state, gender, and board certification. Using the most recent U.S. Census data, information was gathered about each surgeon's county: population, per capita income, and population density (population/mile^2). The population of a county is then divided by the number of surgeons in that county as a proxy for work demand per surgeon (population/surgeon), which is an inverse measurement of surgeon density. Pearson coefficients were obtained at baseline and then stratified for each available demographic factor. Differences between Pearson coefficients were tested via Fisher r-to-z transformation for significance.

Results: When comparing population/surgeon to per capita income, there is a statistically significant inverse relationship (r = -0.0303, p < 0.0001, Figure). In counties with lower income, the work demand per surgeon is higher; for each $5000 decrease in per capita income, population/surgeon increases by 1001. When comparing population/surgeon to population density, there is again a statistically significant inverse relationship (r = -0.0197, p = 0.0014, Figure), suggesting in less densely populated counties the work demand per surgeon is higher. The magnitude of these correlations is enhanced by different demographic factors. Surgeons who are younger (<48 years) are more likely to be in areas with higher per capita income and population density (r = -0.0840, p<0.0001; r = -0.0539, p=0.01). When examining Census regions separately, orthopaedic surgeons are concentrated within wealthier and more densely populated counties of each Census region than is seen nationally, with exception of the Midwest, where per capita income and population density do not affect surgeon geographic distribution as much (income p=0.0324; population density p=0.02). Female surgeons tend to practice in areas with higher population density, although not significantly (p = 0.06), and they are evenly distributed based on per capita income (p=0.47).

Conclusion: U.S. orthopaedic surgeons choose to practice in areas with higher per capita income and higher population density. These effects are more significant among younger surgeons, suggesting the pattern may intensify in the future which can exacerbate the imbalance between patient demand and surgeon supply in lower income and less densely populated areas.

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Distribution of Costs in a Patient Population Under a Global Budget

James Isaacs

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Co-Authors: George Weyer MD; Liz Johns MA; Roman Feygin MBA; Alex Emmitt MPH; Lisa Vinci MD, MS

Background: Alternative payment methods seek to reward providers for high quality care over the entire spectrum of health rather than for the quantity of care measured by single medical encounters. The University of Chicago primary care group is utilizing an alternative payment method by taking on a global budget for a group of Medicare Advantage patients, starting in 2015. This contract uses hierarchical condition categories (HCC) scores to generate a monthly capitated payment for each patient. This score takes into account patient demographics and medical conditions that a patient has in an index year to predict total costs in the next year.

Methods: This was an analysis of how a capitated contract would have worked if it were done in 2014. The actual costs from 2014 were compared to what the capitated rate would have been based off of HCC scores that were calculated from 2013 claims. We then determined a subgroup of patients that had significantly higher actual costs than were predicted by the HCC score.

Results: There were 22 patients (8%) that had actual 2014 costs that were more than $5,000 above the capitated costs that would have been paid based off of the HCC score. The total losses from these 22 patients were $643,934.53. This accounted for 96.9% of the total losses. Of the 22 patients, 18 had only one main condition that contributed to the vast majority of their costs, while 4 patients had multiple conditions that contributed to the majority of costs. Among this group of 22 patients, 9 sought care for the first time at the University of Chicago within 5 years of 2014 in order to see a specialist provider.

Conclusion: A very small portion of the patients accounted for nearly all of the revenue loss under the capitated payment system. For most of these high utilizing patients, there was only one medical problem that contributed to the vast majority of costs. Costs were very focused on high cost services such as cancer and planned surgeries, so the ability to reduce these costs may be limited. However, it is expected that very high utilizing patients will skew medical costs. For global payment to work there must be large number of "complex" patients with high HCC scores whose multiple conditions are well controlled and not yet severe enough to require intensive high cost medical treatment. It is likely that at a tertiary care academic center there is adverse selection as patients with very advanced stage of disease come for specialty treatment, and then join the primary care group. Better investment in Primary Care will create a case mix that has complex patients across a broader spectrum of disease severity, which will be more stable under a global budget.

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Predicting Heart Failure Readmissions Using a Simplified, Actionable Model

Adam Vohra

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**Co-Authors:** Hyuna Yang, PhD; Yizhen Dong; Kristin Francoz; Ai Nguyen; Katerina Steele; Pat Ward; Dan Adelman, PhD; Rupa Mehta Sanghani, MD; Corey Tabit, MD, MBA, MPH; Kirk Spencer, MD

**Background:** Heart failure is the leading cause of hospitalization for patients over 65 years old in the United States. Furthermore, beginning in 2012, the Centers for Medicare & Medicaid Services began penalizing hospitals for excess readmissions in a number of conditions, including heart failure. A number of risk scores have been created to predict which patients are at high risk of readmission, yet most are cumbersome to use and often rely on variables only available at the time of discharge. This study aimed to create a simplified and actionable risk score that could predict heart failure readmission with variables readily available at the time of admission.

**Methods:** Clinical data was gathered through electronic medical records and administrative data for 7,000 patients at an urban academic medical center. Readmission rates were calculated using patients admitted to the hospital for any cause within 30 days of discharge from an index admission due to heart failure using International Classification of Disease-9 (ICD-9) Clinical Modification codes. Variables were selected using forward stepwise logistic regression, lasso regression, and random forests. In each method, 1000 models were fitted by conducting 5-fold cross-validation. An aggregated proportion was calculated based on the frequency variables were selected in each of these models with only models whose performance was greater than average. Three models were then fitted: 1) all 36 initial variables, 2) 8 continuous variables chosen by frequency of selection and clinical expertise, 3) 8 binary variables chosen by frequency of selection and cutoff values determined by prior literature and recursive tree partitioning.

**Results:** Seven thousand patients and 36 variables were analyzed to predict heart failure readmission. The final model included eight variables encompassing demographics, medications, laboratory data, and vitals (hemoglobin, serum sodium, heart rate, pulse, medication count, Medicaid payer, non-elective admission, and discharged on digoxin). Out-of-sample, the sensitivity of the 8-variable binary model was 0.55 and the specificity was 0.81 with the area under the receiver operator characteristic curve (AUC) at 0.60. The full 36-variable model produced a sensitivity of 0.60, specificity of 0.80, and AUC of 0.61.

**Conclusion:** The model created by this study predicted heart failure readmissions on par with published literature with only eight, binary variables. Our study showed that only eight, binary variables were nearly as predictive as a full model consisting of 36 variables. The 8 final variables were chosen based on predictive power, and may not represent a causal effect. Furthermore, all but one of these variables was available at the time of admission, allowing health care practitioners to provide appropriate assessment, education, and treatment during the inpatient admission to help prevent readmission.

**Acknowledgements/Disclosures:** The University of Chicago Calvin Fentress Fellowship Recipient.
National Economic Conditions and Patient Insurance Status Predict Prostate Cancer Diagnosis Rates and Management Decisions

Adam Weiner

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*Co-Authors:* Rena M. Conti, PhD; Scott Eggener, MD

**Background:** The recent "Great Recession" from December 2007 to June 2009 was the largest economic contraction since the Great Depression during which 25% of Americans reduced health care usage. Prostate cancer (PCa) is prevalent in the U.S. population and there are significant cost differences between conservative management (CM) and active treatment. We hypothesize the national incidence of non-palpable prostate-specific antigen (PSA) screen-detected PCa decreases and the use of CM for non-palpable PCa patients increases during periods of national economic hardship.

**Methods:** We derived national, monthly diagnosis rates and use of CM for screen-detected, non-palpable PCa and patient-level insurance status from the Surveillance, Epidemiology and End Results database (2004-2011) and monthly statistics on national unemployment rates, inflation, median household income, and S&P 500 closing values from government sources. Diagnosis rates were standardized to Census Bureau yearly, adult male population estimates. Using linear multivariable regression, we measured the correlation between national macroeconomic conditions and two outcome variables 1) PCa diagnoses and 2) use of CM. A Bonferroni correction for four outcome variable was used and thus a p-value<0.05/4=0.0125 was considered significant. Using logistic multivariable regression, we analyzed the association of various patient level variables with CM use to determine if being insured by Medicaid or uninsured increased use of CM. To characterize how the association of each independent variable changed when patients were diagnosed during the "Great Recession" months, we used non-pooled regressions for each independent variable which included an interaction term of being diagnosed during the "Great Recession" months. A p-value<0.05 was considered significant for these regressions.

**Results:** Diagnosis rates of screen-detected PCa correlated positively with a marker of thriving economy, S&P 500 monthly close (coefficient=24.90, 95% CI 6.29 to 43.50, p=0.009). CM use correlated negatively with a marker of thriving economy, median household income (coefficient=-49.13, 95% CI -69.29 to -28.98, p=0.001). Among a non-Medicare eligible population, having Medicaid (OR 1.51, 95% CI 1.32-1.73, p<0.001) or no insurance (OR 2.27, 95% CI 1.93-2.67, p<0.001) compared to private insurance increased use of CM compared to men with private insurance. Being of non-Hispanic Black was also associated with increased CM used (vs. non-Hispanic White race; OR 1.69, 95% CI 1.57-1.82, p<0.001). As indicated by a significant positive interaction term, being diagnosed during the "Great Recession" increased the associations of Medicaid insurance and Black race with CM use (OR 1.30, 95% CI 1.02-1.68, p=0.037 and OR 1.15, 95% CI 1.01-1.30, p=0.032).

**Conclusion:** National economic hardship was associated with decreased diagnosis rates of non-palpable PCa and increased use of CM. Being of Black race or not having private insurance was associated with CM use, especially during the "Great Recession."

**Acknowledgements/Disclosures:** Prostate cancer (PCa), conservative management (CM), Odds ratio (OR), Confidence interval (CI); The University of Chicago John D. Arnold, MD Scientific Research Prize Recipient.
Scientific Investigation in Basic Sciences
Continuous Adductor Canal Blockade after Primary Total Knee Arthroplasty: A Prospective, Randomized Controlled Trial

Sahitya Denduluri

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Co-Authors: Patrick Leung, MD; Maryam K. Mohammed, BS; Min Lu, MD; David Dickerson, MD; Magdalena Anitescu, MD, PhD; Hue Luu, MD

Background: Various analgesic techniques have been described for total knee arthroplasty (TKA). Continuous epidural analgesia with subsequent continuous adductor canal block (cACB) has not been studied. We hypothesized that such a preventative analgesic regimen could reduce pain and improve function after TKA when compared to epidural alone.

Methods: After IRB approval, patients were enrolled and scheduled for unilateral primary TKA with the same surgeon. Subjects were block randomized into treatment (cACB catheter) and control (sham catheter) groups. All patients received an epidural catheter preoperatively, which was discontinued on post-operative day (POD) 1. Patients then received either an ultrasound-guided cACB or sham catheter. Catheters were connected to a concealed infusion, but only treatment catheters were infused with solution (0.125% bupivacaine). Patient blinding was accomplished by opaque dressings, opaque draping that prevented observation of catheter placement and, in the control group, 10 seconds of significant pressure with a wooden applicator. The study catheter was discontinued on the morning of discharge, typically POD 2. Daily range of motion (ROM) and ambulation distances were recorded by physical therapy. Patients filled out the WOMAC osteoarthritis questionnaire before surgery and at each follow-up visit, and were also administered a post-discharge phone interview regarding satisfaction. With exception of the anesthesia pain service, all medical/research personnel were blinded. Statistics were performed using Microsoft Excel.

Results: Of 130 enrolled patients, 52 completed the inpatient portion of the study. Common reasons for subject removal were: voluntary withdrawal, epidural catheter failure, general anesthesia requirement, and inadvertent protocol violation. At baseline, ROM was lower in the treatment group (p = 0.03), but no other differences were observed. With epidural infusing at 12 hours postoperatively, visual acuity scale (VAS) pain scores (area under the curve [AUC]) and cumulative opioid usage (in morphine equivalents) were not different between groups. At 20 hours after study catheter placement, VAS AUC and cumulative opioid consumption were significantly lower in the treatment group compared to the control group (p = 0.04 and p = 0.03, respectively). Due to baseline differences, the treatment group continued to have lower ROM on POD 1 compared to the control group, but the difference was no longer apparent by POD 2. There were also no differences in length of hospital stay and ambulation distances (at any time point) between groups. Satisfaction with pain control was also the same for both groups. Though no differences were observed at baseline, WOMAC scores at 3-week follow-up appointment were significantly better in the treatment group compared to control (p = 0.01). No differences were seen at the 6-week follow-up appointment (p = 0.14).

Conclusion: Following TKA, transitioning from epidural analgesia to continuous adductor canal block may not only decrease pain and opioid medication usage in the hospital, but also improve short-term functional status.

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Evidence of Electrophysiological Activity of Motor Cortex Contralateral to Amputated Limb Exhibiting $\beta$-Oscillation Attenuation and Providing Command Signals to Centrally-Implanted Brain Machine Interfaces.

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Background: Whether signals originating from deafferented and deafferented cortices contralateral to an amputated limb have the capacity to serve as signal-sources for centrally-implanted Brain-Machine-Interfaces (BMIs), has not been well-established. We characterize this neural-interface by conducting a spectral analysis of the signal acquired via two distinct recording modalities, cortical-surface microelectrocorticography (ECoG) and intracortical-multielectrode-arrays (iMEAs). In particular, we focus on $\beta$-oscillatory-activity, as it is a well-characterized frequency-band modulated by motor behavior. To that end, we investigate whether micro-ECoG and MEA local-field-potentials (LFPs)—obtained from adjacent, functionally- and cytoarchitecturally-distinct cortical regions—exhibit modulation of $\beta$-oscillatory-activity during robotic-arm manipulation by comparing sequential Idle and Velocity-encoding epochs.

Methods: A single-amputee, female Macaque monkey—implanted with a micro-ECoG in PMv and an MEA in M1—performed an iterative-reach paradigm that involved reaching a target object with a Whole-Arm-Manipulator. The decoder linked to a 96-channel MEA M1 cortical-spiking activity contralateral to the amputated limb, and an adjacent 32-channel micro-ECoG located in PMv, S1, and M1.

Results: Source-signals decoding for velocity values 2.5% of baseline or less were treated as Idle epochs, and those exceeding 2.5% of baseline-velocity values were treated as Velocity-Encoding epochs. Trials consisted of 1000-ms of data in which 500-ms of Idle preceded 500-ms of Velocity-encoding (490 trials from a single experimental-session). Velocity Encoding trial-averaged $\beta$-power as a function of Idle trial-averaged $\beta$-power for both ECoG and MEA demonstrated $\beta$-attenuation in most channels during Velocity-encoding (binomial-CDF-test: MEA & ECoG p<0.001; MEA & ECoG R2>0.98). Velocity-encoding $\beta$-power for single-trials as a function of Idle $\beta$-power for single-trials of both ECoG and MEA featured $\beta$-attenuation in most channels during Velocity-encoding (binomial-CDF-test: MEA & ECoG p<0.01) trended toward greater $\beta$-power in Idle states (ECoG: R2=0.35; MEA: R2=0.25). Wilcoxon-signed-rank test revealed attenuation (p<0.01) of $\beta$-power during Velocity-encoding epochs in 21/32 ECoG channels and 19/96 MEA-channels relative to respective preceding Idle epochs, despite trial-to-trial variability.

Conclusion: Signals sourced from arm-hand areas of motor-cortex contralateral to an amputated forelimb serve as the neural-interface for robotic-arm-manipulation. Despite years of probable motor-cortical reorganization, the motor-cortex exhibits characteristic $\beta$-oscillatory activity and task-induced modulation. Our data discounts the hypothesis that attenuated $\beta$-oscillatory activity during epochs of sustained velocity-encoding is dependent on sensorimotor-feedback. Future directions include investigating the spectral coherence between ECoG and MEA signals, and longitudinal changes in magnitude of oscillatory activity modulation evident across training sessions.

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Cancer Therapies Activate RIG-I-Like Receptor Pathway Through Endogenous Non-Coding RNAs

Akash Parekh

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Background: Emerging evidence indicates that ionizing radiation (IR) and chemotherapies activate Type I interferon (IFN) signaling in tumor and host cells. However, the mechanism of induction is poorly understood. We identified a novel radioprotective role for the DEXH box RNA helicase LGP2 (DHX58) through its suppression of IR-induced cytotoxic IFN-beta [1]. LGP2 inhibits activation of the RIG-I-like receptor (RLR) pathway upon binding of viral RNA to the cytoplasmic sensors RIG-I (DDX58) and MDA5 (IFIH1) and subsequent IFN signaling via the mitochondrial adaptor protein MAVS (IPS1).

Methods: To determine the role of the RLR system in IR induced Type I IFN signaling, we performed ELISAs for IFN-Beta protein secretion in WT MEFS (C57BL/6), MAVS-/- MEFs, and RIG-I-/- MEFs 48 hours following exposure to increasing doses of IR, and following IR exposure of MAVS-/- MEFs and RIG-I-/- MEFs reconstituted by transient transfection of a full-length human MAVS construct or RIG-I construct. We additionally looked at IR-induced IFN-beta following siRNA-mediated suppression of MAVS, RIG-I, and MDA-5 in human D54 glioblastoma cells. To investigate the RLR pathway role in mediating radiation-induced gastrointestinal death following total body irradiation, we calculated overall survival following total body irradiation (5.5 Gy) of age-matched WT and germline deleted LGP2-/-, RIG-I-/-, and MDA5-/- mice. To determine whether IR induces RIG-I binding to endogenous double-stranded RNAs, HEK293 reporter cells were irradiated after transfection with either an empty vector, a full length human RIG-I, a RIG-I lacking CARD domains, or a RIG-I harboring K858A and K861A mutations in the C-terminal domain, in addition to an IFN-beta promoter-driven luciferase construct. To determine if RIG-I binds U1 snRNA accumulated in the cytoplasm, we employed a pull down method to elute total RNA and RNA bound to FLAG-tagged full-size RIG-I from RIG-I over-expressing HEK293 cells 48 hours post 6Gy IR. RNA purified were sequenced on Illumina HiSeq2500 to determine top hits.

Results: We demonstrate that MAVS is necessary for IFN-beta induction and interferon-stimulated gene expression in the response to IR. Suppression of MAVS conferred radioresistance in normal and cancer cells. Germline deletion of RIG-I, but not MDA5, protected mice from death following total body irradiation, while deletion of LGP2 accelerated the death of irradiated animals. In human tumors depletion of RIG-I conferred resistance to IR. Mechanistically, IR stimulated the binding of cytoplasmic RIG-I with small endogenous non-coding RNAs (sncRNAs), which triggered IFN-beta activity.

Conclusion: These findings suggest that the physiologic responses to radio therapy converge on an antiviral program in recruitment of the RLR pathway by a sncRNA-dependent activation of RIG-I. To our knowledge, this is the first demonstration of a cell-intrinsic response to clinical genotoxic treatments mediated by an RNA-dependent mechanism.

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Associations of FGF8 with the Olfactory Bulb: Lineage Tracing and Specification of Cell Fate

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Co-Authors: Stavroula Assimacopoulos, MS; Elizabeth Grove, PhD

Background: The ways in which telencephalic structures are induced and patterned remains a major question in developmental neurobiology. One structure, the olfactory bulb is a critical component of the olfactory system. It has been shown that mice and humans with mutations in Fgf8 present with rudimentary or absent olfactory bulbs. However, the precise role of Fgf8 in olfactory bulb patterning has yet to be resolved. We hypothesized that 1) one or more olfactory bulb cell types are derived directly from the anterior FGF8 signaling center, 2) that cell fate specification of these cell types is finely regulated by local levels of secreted FGF protein, and 3) that overexpression of Fgf8 is sufficient to induce genetically identifiable olfactory bulb cell types in ectopic regions of the cerebral cortex.

Methods: To test 1) if one or more olfactory bulb cell types are derived from the anterior source of FGF8, an Fgf8-IRES-Cre X ROSA mouse line was used to fate map the Fgf8 lineage in mouse brains at E10.5, P0 and P14 using immunohistochemistry. To test 2) if specification of olfactory bulb cells occurs in a threshold dependent manner, an Fgf8 +/- ; Fgf17/-/- compound mutant mouse line was examined with in situ hybridization for morphological changes compared to control lines. To test 3) if ectopic Fgf8 expression is sufficient to induce patterns of gene expression specific to olfactory bulb cell types, we performed in utero microelectroporation of EF1-Fgf8b DNA into the telencephalic hemispheres of E10.5 mice and analyzed by in situ hybridization for mitral cell specific genes including AP2e and Scg2 at E12.5.

Results: Our data show that 1) At E10.5, immunohistochemistry reveals cells in the anterior telencephalon, extending into the olfactory bulb. At P0, staining shows cells organized into a cellarily dense and organized layer. At P14, the labeled cells show mitral cell morphology and have extended long dendrites into appropriate regions of the adjacent olfactory bulb. The data also show 2) that the Fgf8 +/- ; Fgf17/-/-mutants had a thinner mitral cell layer at P6 but maintain a comparable olfactory bulb size. Finally, the data show 3) that expression of mitral cell markers AP2e and Scg2 is induced following electroporation of EF1-Fgf8b into non-olfactory regions of the telencephalon.

Conclusion: Our results support our hypotheses by demonstrating that 1) mitral cells develop from progenitor cells inside the source of FGF8, 2) reductions in FGF signaling leads to a reduction of mitral cells in the olfactory bulb indicating that high local FGF signaling is necessary and 3) high levels of FGF8 are sufficient to ectopically induce cells that biochemically and structurally resemble mitral cells. Taken together, our data illustrate that Fgf8 is critical for general patterning of the telencephalon and is necessary and sufficient for cell fate specification during olfactory bulb development.

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Structural Polymorphisms of Amyloid in Alzheimer's Disease and Cerebral Amyloid Angiopathy

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Background: Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA) are characterized by the accumulation of insoluble amyloid fibrils composed of Aβ peptide in the brain parenchyma and vasculature, respectively. Aβ fibrils share a common β-sheet architecture, but in contrast to competently folding proteins, Aβ forms polymorphic aggregates, the structures of which depend on fibrillization conditions as well as sequence. A variety of structures for purely in vitro Aβ fibrils have been published, some of which differ in biological properties such as toxicity, as well as structure and stability. In vitro studies have shown a prion-like property of Aβ: the addition of preformed Aβ fibril ‘seeds’ to monomeric Aβ induces the formation of replicate fibrils. Recently, the structures of synthetic Aβ fibrils seeded by AD brain tissue of four patients were studied and found to be different from any previously-described purely in vitro fibrils. Although differences in structure were found between patients, no differences in fibril structure were found in different regions of a single person’s brain. This research contributes to the study of amyloid structure in several additional AD patients, and expands on prior investigations by including CAA patients and murine AD models as well.

Methods: Insoluble Aβ aggregates were isolated biochemically from the brains of persons who died with AD alone, CAA alone, or AD with CAA, and used as templates for the formation of brain-structured fibrils from synthetic Aβ peptide, with or without isotopic labeling. These brain-seeded fibrils were studied by solid-state (ss) NMR, X-ray diffraction, and electron microscopy. Brain extracts from APP/PS1 AD model mice and control mice were also used as seeds for synthetic fibrils.

Results: C-terminus labeled Aβ fibrils (V24, G25, A30, I31, L34, M35) seeded from the vascular deposits of three patients with both AD and CAA were studied by ssNMR, and significant polymorphisms were noted, particularly at residues V24 and I31. N-terminus labeled Aβ fibrils (A2, F4, G9, V12, Q15, L34) seeded from parenchymal or vascular deposits of patients with CAA only (one patient), or AD and CAA (three patients), were prepared. No intra-patient differences were noted in the fibrils seeded from parenchymal vs vascular aggregates from patients with ADD and CAA. The X-ray diffraction spectra of brain-seeded fibrils included reflections not normally seen in synthetic Aβ fibrils, indicating increased structural order. Isolates from murine brain tissue were unable to seed fibril formation.

Conclusion: AD and CAA share features with prion diseases. Only one or a few Aβ structures are observed in a given patient’s brain, although in vitro Aβ forms a variety of structures, suggesting that once a particular fibril type forms, it is spread throughout the brain. In particular, there is no evidence of different structures between parenchymal and vascular amyloid intra-patient. Both ssNMR and X-ray diffraction data suggest that the fibrils which form in vivo are highly ordered. Finally, Aβ fibrils in murine models of AD may be structurally distinct from human Aβ fibrils, given their different biochemical behaviors.

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Positive and Negative Signaling through SLAM Receptors Regulate Immune Synapse Organization and Thresholds of Cytolysis

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**Co-Authors:** Jennifer Cannons, PhD; Mala Dutta, PhD; Gillian Griffiths, PhD; Pamela Schwartzberg, MD, PhD

**Background:** Cytotoxic T lymphocytes (CTLs) kill virally infected and tumorigenic cells through the regulated secretion of cytolytic granules. This requires T cell receptor (TCR) recognition of cognate peptide-MHC class I on target cells, which triggers downstream signaling and the formation of a distinct topological structure at the CTL-target cell interface known as the immunological synapse (IS). A concurrent polarization of the centrosome leads to the reorientation of the microtubule cytoskeleton toward the target cell. This allows the targeted movement of granules along microtubules toward the docked centrosome, where they fuse at a distinct secretory domain on the plasma membrane, releasing their cytolytic components into the target cell. Mutations affecting the adaptor SAP, which links SLAM family surface receptors to downstream signaling, cause massive immune dysregulation in patients with X-linked lymphoproliferative syndrome type 1 (XLP1). It is characterized by fatal responses to Epstein-Barr virus (EBV) infection, development of lymphomas, hypogammaglobulinemia, and hemophagocytic syndrome. Although abnormalities in NK and T cell function are documented, the mechanism behind defective CTL activity against EBV-infected B cells remains unclear.

**Methods:** To dissect the requirements for SAP in CTL function under defined conditions, we utilized the OT-I TCR transgenic mouse model, which expresses a clonal TCR recognizing the specific ovalbumin peptide SIINFEKL in the context of H-2Kb. This system permitted comparison of cytolysis of different cellular targets by WT and SAP-deficient CTLs with the same well-defined antigen. Using immunofluorescence confocal microscopy, we examined early events in IS organization and signaling, as well as downstream polarization of the centrosome and granules. Studies on protein interactions and in vitro rescue of cytolytic function by SHP-1 inhibition were performed to definitively link altered signaling to impaired cytolysis by SAP-deficient CTLs.

**Results:** We show that SAP-deficient murine CTLs exhibited normal cytotoxicity against fibrosarcoma targets, yet had impaired adhesion to and killing of B cell and low-avidity T cell targets. SAP-deficient CTLs showed specific defects in IS organization with these targets, resulting in inefficient actin clearance and centrosome docking. In the absence of SAP, signaling through the SLAM family members Ly108 and 2B4 resulted in increased recruitment of the SHP-1 phosphatase and reduced SHP-1 clearance at the synapse. This was associated with decreased activation of Src kinases and tyrosine phosphorylation, some of the earliest events in IS formation. Conversely, when SAP was expressed, Ly108 engagement augmented TCR-mediated signals and enhanced cytolytic function.

**Conclusion:** By affecting the recruitment of Src family kinases and phosphatases, positive and negative signaling through SLAM family receptors play an indispensable role in modulating IS formation. This system provides a critical feature of immunoregulation required for normal lymphocyte interaction and function. The importance of this regulation is highlighted by the profound phenotypes of XLP1.

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Scientific Investigation in Clinical Research or Social Sciences
Novel Autoantibody Systems in Systemic Lupus Erythematosus: IgG and IgA Anti-Vimentin

Rene Bermea

**Mentor:** Marcus R. Clark, MD, Department of Medicine, Section of Rheumatology

**Co-Authors:** Andrew J. Kinloch, PhD; Marcus R. Clark, MD

**Background:** Systemic Lupus Erythematosus (SLE) is a multi-organ autoimmune disease whose most important predictor of mortality is renal involvement in the form of lupus nephritis (LN). No clinical assay currently exists that predicts the presence or risk of progression to LN and biopsy-driven classification criteria poorly predict survival outcomes. Our lab has identified autoantibodies to the cytoskeletal protein vimentin generated "in-situ" in the tubulointerstitium of subjects with LN via tertiary lymphoid organs. We have since developed an assay to detect anti-vimentin antibodies (AVAs) in the serum. The aims of this study are to determine which isotypes of AVA are present in subjects with SLE, assess whether AVAs are independent of other common rheumatic markers, and establish AVA thresholds that predict biopsy characteristics in subjects with lupus nephritis.

**Methods:** Serum, demographic data, common rheumatic serologies, and renal biopsies (if available) were collected from 99 subjects with SLE. AVA titers were determined by ELISA. To study if AVAs were independent autoantibody systems, correlation analyses were done between AVA isotypes and common rheumatic markers (RF, dsDNA, Ro, La, Sm, RNP). Arbitrary "positive" and "negative" AVA AU cut-offs were used to generate sensitivity, specificity, PPVs, NPVs, and LRs for proliferative lupus nephritis and tubulointerstitial inflammation scores greater than zero.

**Results:** A wide range of AVA AUs were found in both the IgG and IgA isotype. No such range was appreciated in the AVA IgE isotype. High levels of IgG AVA titers did not correspond to high IgA titers and vice-versa, although the correlation between the two was significant (r=0.3571, p =0.0003). Similarly, subjects with high IgG (r=-0.05239, p=0.6122) and IgA (r=0.2912, p=0.0033) AVAs were not found to have high RF titers of the same isotype. When compared to other common rheumatic serologies, IgG AVAs did not correlate with most and IgA AVAs did not correlate with any. Using arbitrary cut-offs, IgG and IgA AVAs were both positively-predictive of proliferative glomerulonephritis (PPV = 87.5% and 90.9%, respectively). IgG AVA was also positively-predictive of tubulointerstitial scores greater than zero (PPV = 92.3%).

**Conclusion:** These data suggest that AVAs are novel autoantibodies in SLE and exist as at least two isotypes (IgG and IgA). IgG AVAs and IgA AVAs are independent of one another and other common rheumatic markers, suggesting that these antibodies are generated through separate pathological pathways. Assays for AVAs may be a clinically useful tool in the future, with early results showing that they can be positively-predictive and specific for proliferative lupus nephritis and tubulointerstitial inflammation. Our AVA assay yields information that current clinical assays do not. With more data, this assay may prove to be sufficient for establishing the diagnosis and prognosis of lupus nephritis without biopsy.

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Predicting Progression in Barrett's Esophagus – Development and Validation of the Barrett's Esophagus Assessment of Risk Score (BEAR Score)

Craig Brown

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Background: Endoscopic therapies have emerged capable of eradicating BE with high efficacy and low complication rates, but which patients should receive treatment is still debated.

Methods: We retrospectively collected data from a cohort of 2591 BE patients over a 13-year period. Patients were randomly separated into training (75%) and validation (25%) groups. Coefficients from a multivariable logistic regression model of training group patients were used to develop a simplified risk of progression score (ROP). We then validated the scores ability to predict progression in the remaining 25%.

Results: The training cohort included 1943 BE patients of which 99 progressed to dysplasia/adenocarcinoma. Multivariable analysis resulted in five variables associated with an increased risk of progression (age ≥ 75, male gender, lack of PPI use, segment > 3cm, and history of esophageal candidiasis). Using this model, we developed a simple ROP score with possible values between 0 and 8. ROC analysis showed a cutoff of ≥ 3 to have a sensitivity and specificity of 68% and 80%, respectively, with a c-statistic of 0.79. When applied to a validation group of 648 patients, of which 34 progressed, the score was capable of differentiating patients at high risk of progression with a sensitivity and specificity of 76% and 80%, respectively. Patients with a score ≥ 3 had OR of 8.74 (95% CI 5.53-13.81) and 12.21 (95% CI 5.36-27.83) for the training and validation cohorts, respectively.

Conclusion: Our data show the development and internal validation of the Barrett's Esophagus Assessment of Risk Score (BEAR Score) as capable of quantifying the likelihood of progression to dysplasia/adenocarcinoma.

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Afatinib Activity in Platinum-Refractory Metastatic Urothelial Carcinoma In Patients With ERBB Alterations

Noura Choudhury

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Background: Urothelial carcinoma (UC) remains the eighth-leading cause of cancer death in the United States, with 16,000 deaths expected in 2015. Despite nearly universal fatality in metastatic, platinum-refractory disease, there are no approved second-line therapies. Somatic mutations and copy number variation in the ERBB family (EGFR, HER2, ERBB3, and ERBB4) are frequent in UC and may represent viable therapeutic targets. We studied whether afatinib, an oral, irreversible ErbB family inhibitor has activity in UC and if specific ERBB molecular alterations are associated with clinical response.

Methods: In this single-arm phase II trial, patients with metastatic platinum-refractory UC received afatinib 40 mg/day continuously until progression or intolerance. The primary endpoint was three-month progression-free survival (PFS3). The major secondary endpoint was pre-specified biomarker analysis for molecular alterations in the ERBB family, conducted using formalin-fixed, paraffin embedded tumor tissue collected from surgical resections with peripheral blood as germline controls. Deep, targeted next-generation sequencing for alterations in the four ERBB genes was performed on the Ion PGM platform (Thermo Fisher Scientific, Waltham, MA) with Sanger sequencing confirmation of somatic mutations. HER2/EGFR copy number analysis was performed using TaqMan copy number assays (Thermo Fisher) on the ViiA 7 Real-Time PCR System (Applied Biosystems). Statistical analyses were performed using GraphPad Prism 6.

Results: The first-stage enrollment goal of 23 patients was met. There were no statistically significant differences between responders and non-responders in terms of prognostic characteristics. No unexpected toxicities were observed. Overall, 5/23 patients (21.7%) met PFS3 (2 partial response, 3 stable disease). Notably, among the 21 tumors analyzed, 5/6 patients (83.3%) with HER2 and/or ERBB3 alterations achieved PFS3 (PFS=10.3, 7.0, 6.9, 6.3 and 5.0 months respectively) versus 0/15 without alterations (p<0.001, Fisher's exact). 3/4 patients with HER2 amplification and 3/3 patients with ERBB3 somatic mutations (G284R, V104M, R103G) met PFS3. One patient with dual HER2 amplification and ERBB3 mutation never progressed on therapy, but discontinued after 10.3 months due to depressed left ventricular ejection fraction. Median time to progression or discontinuation was 6.6 months in patients with HER2 and/or ERBB3 alterations versus 1.4 months in patients without alterations (p<0.001, log-rank test).

Conclusion: Afatinib demonstrated significant activity in platinum-refractory UC patients with HER2 and/or ERBB3 alterations. The median PFS of 6.6 months among patients with alterations is nearly three-fold longer than historical PFS times reported for second-line agents investigated in this disease setting. This represents the first report of biomarkers specific for afatinib in UC. The potential contribution of ERBB3 to afatinib sensitivity has also not been previously described.

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Histological Diagnosis Of Pediatric Optic Nerve Gliomas

Joshua Eassa

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**Co-Authors:** Sandi Lam, MD, MBA

**Background:** Optic Nerve Gliomas (ONGs) are rare pediatric neoplasms, composing 0.6-1.2% of intracranial tumors and 1.7-7% of gliomas, with 59-70% presenting before age ten. Most literature consists of single institution reports. Histologically, ONGs are generally low grade astrocytomas, which are typically benign, but can enlarge and cause symptoms, or invade other areas of the CNS, with unpredictable natural history. The course of the tumor is variable with progression, recession, and stability all possible outcomes. Nevertheless, prognostic factors have not been well described and no standard management consensus exists. Often, the tumor is biopsied or resected surgically with histologic diagnosis, but the necessity of this is debated since ONGs have characteristic radiographic appearance and surgery carries risk. This study looks for prognostic factors that predict whether histological diagnosis (suggestive of surgical intervention) was used, which will hopefully provide insight regarding the best course of diagnosis and management.

**Methods:** Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) program (1973-2008). SEER consists of data from 17 areas of the United States and represents approximately 26% of the population. Site and histology codes of the International Classification of Disease for Oncology (ICD-03) were used to identify cases. Only pediatric patients (0-18 years) were included. Covariates included are categorical age at diagnosis, sex, race, ethnicity, radiation therapy, surgery, diagnosis date, and sequence of surgery and radiation treatment. The associations of variables with histological diagnosis and with surgery were quantified using chi-squared analysis. A p value of <0.05 was considered statistically significant. The statistical analyses were carried out using STATA version 12.

**Results:** Over 75% of patients were aged one to nine, with approximately equal numbers male and female. Most patients were non-Hispanic Caucasians. 68.05% were histologically confirmed, with 72.93% being malignant gliomas and 21.71% being pilocytic astrocytomas. Chi-squared analysis showed that age, sex, race, ethnicity, tumor size, and radiation were not correlated with histological diagnosis, but surgery and diagnosis date were (p < 0.01). Additionally, diagnosis date, histological confirmation, and location all were correlated with whether a patient had surgery (p<0.01).

**Conclusion:** ONGs have been studied as case reports and series, but few have looked at ONGs comprehensively. ONGs are rare pediatric tumors that typically have good survival. While, some ONGs are diagnosed histologically, surgical procedures may be associated with morbidity such as vision loss. Some neuro-ophthalmologists believe NF-1 and MRI evidence of ONGs is sufficient for diagnosis. The current study found that surgery and diagnosis date are predictive of histological diagnosis. This suggests higher use of surgical intervention in more recent years. Diagnosis date, histology, and study site are predictive of surgery indicating that possible differences in technology over time or medical practice by region determine if a patient receives surgery, not patient or tumor characteristics. The strength of the present study is due to a large sample size from the nationwide SEER database. However, there are also limitations. SEER does not provide detailed patient and treatment-related factor data, and outcome data is limited to mortality.

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Surgical Intervention for High-Grade Vesicoureteral Reflux in a Single-Surgeon Practice: Extravesical Robotic or Intravesical Open?

Prithvi Murthy

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**Co-Authors:** William R. Boysen, MD; Mohan Gundeti, MD

**Background:** Extravesical robotic assisted laparoscopic ureteral reimplantation (RALUR-EV) is becoming increasingly utilized at specialized pediatric urologic centers. Single-surgeon comparisons of RALUR-EV, along with technical modifications over the course of the learning curve, and the conventional open intravesical ureteral reimplantation (OUR) are limited, prompting this study.

**Methods:** We performed a retrospective chart review of all patients undergoing RALUR-EV and OUR by a single surgeon (MSG) between July 2008 and October 2015, analyzing only patients with primary vesicoureteral reflux (VUR). Surgical indications included breakthrough febrile UTIs, worsening/high grade VUR (Grade IV or V), renal scarring on radioisotope renography, or lack of spontaneous resolution by age five. Patients underwent RALUR-EV based on surgeon comfort with body habitus, age and procedural experience. Surgical success was defined as resolution of reflux on post-operative voiding cystourethrogram. RALUR-EV technique modifications were implemented based on prior operative video analysis. Non-parametric statistics were employed.

**Results:** 78 patients (61 RALUR-EV: 84 ureters; 17 OUR: 23 ureters) met our inclusion criteria, totaling 107 ureters. The laterality and number of bilateral surgeries did not differ between groups. The RALUR-EV cohort was older (5.0yrs vs 3.2yrs, p=0.03). There was no difference in operative time between cohorts (RALUR-EV 153 min., OUR 150 min, p=0.27), though Robotic groups 1 (195 min.) and 2 (213 min.) had longer operative times than the OUR group or Robotic group 3 (133 min) due to the learning curve. The RALUR-EV group had shorter lengths of Foley catheterization and stay (both 2 days vs. 4 days, p<0.01). The complication rate and severity did not differ by cohort (p=0.07). There were 2 and 1 Clavien Grade III complications (those requiring operative intervention) in the OUR and RALUR-EV, respectively. One OUR patient had clinically significant bladder spasms in the immediate post-operative period, and one RALUR-EV patient experienced urinary retention requiring seven days of catheterization. 8 patients (47%) undergoing OUR required epidural analgesia, compared to none in RALUR-EV. Overall, the ureteral success rate was 69/84 (82%) in RALUR-EV, and 23/23 (100%) in OUR (p=0.04).

**Conclusion:** RALUR-EV may offer a shorter length of catheterization and stay without compromising operative time or complication rates. Success rates do not equal OUR, indicating a long learning curve due to technical refinements.

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Improvement in Cognitive Function in Patients with Relapsing-Remitting Multiple Sclerosis Treated With Natalizumab Occurs In Patients With Shorter Disease Duration

Garrick Talmage

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Co-Authors: Gabrielle Liu; Ben Rincy; Adil Javed, MD, PhD; Jacqueline Bernard, MD

Background: Brain atrophy can occur early in the disease course of Relapsing Remitting Multiple Sclerosis (RRMS), leading to clinical disability and cognitive dysfunction. These changes may be delayed or reduced by natalizumab.

Methods: We completed a prospective 96-week, open-label, single center, single-cohort study at the University of Chicago Medical Center. Twenty patients diagnosed with RRMS were treated with natalizumab for 96 weeks. 3T MRI scans and the Symbol Digit Modalities Test (SDMT) were performed at baseline, week 48 and 96. Expanded Disability Status Scale (EDSS) and Optical Coherence Tomography (OCT) scans were performed at baseline, week 24, 48, 72, and 96.

Results: At baseline, SDMT z-scores were highly correlated with subcortical grey matter volumes, including amygdala ($r = 0.729, p < 0.001$), hippocampus ($r = 0.621, p = 0.003$), and thalamus ($r = 0.577, p = 0.008$) but not whole brain volume. Multiple linear regression of these variables revealed that amygdala volume remained correlated with baseline SDMT z-scores ($r = 0.536, p = 0.032$). Longitudinally, a mixed model found that SDMT z-scores increased over time ($p = 0.036$) and patients with shorter disease durations were more likely to see this increase ($p = 0.032$). Retinal Nerve Fiber Layer thickness measured by OCT was decreased as compared to controls at baseline but did not change over the course of the treatment period.

Conclusion: Baseline atrophy of subcortical grey matter structures involved in information processing and memory is related to cognitive dysfunction. Patients with shorter disease durations had the most cognitive improvement with natalizumab, indicating a potential benefit of using natalizumab early on in an RRMS patient's disease course.

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Long-Term Effects of Anti-VEGF Injections on Intraocular Pressure in Patients with Age-Related Macular Degeneration and Diabetic Macular Edema

Blake Williams

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Co-Author: Ashiyana Nariani, MD; Seenu Hariprasad, MD

Background: There is debate in the ophthalmology community about whether anti-VEGF injections result in a long-term increase in intraocular pressure (IOP). Some studies have identified risk factors (i.e. number of injections, interval between injections) that are associated with elevated IOP, while other studies have shown that intravitreal anti-VEGF injections do not lead to elevated IOP. We performed a retrospective, observational clinical study to investigate how the number and timing of intravitreal injections for patients with age-related macular degeneration (AMD) and diabetic macular edema (DME) affect IOP over time.

Methods: After receiving IRB approval, we collected long-term IOP data on patients receiving anti-VEGF injections at the University of Chicago. Patients over the age of 40 who received the injections for AMD (n = 76) or DME (n = 55) were included in the study; those receiving injections for retinal vein occlusion were excluded. Patients were grouped according to indication for injection as well as number of injections received (1-3, 4-6, 7-9, or 10+ injections). IOP measurements were then placed into time points (0-6, 6-12, 12-18, 18-24, or 24+ months after first injection) and compared to the pre-injection IOP. One-tailed t-tests were used for statistical analysis.

Results: For patients with DME, average initial IOP was 15.7 mmHg. At 24+ months after injection, the average IOP was 15.2 (95% CI: 13.8-16.6, p = 0.68) for patients receiving 1-3 injections, 16.8 (15.3-18.3, p = 0.23) for 4-6 injections, and 14.4 (13.8-15.0, p = 0.66) for 7-9 injections. For patients with AMD, average initial IOP was 15.6 mmHg. At 24+ months after injection, the average IOP was 12.6 (95% CI: 10.8-14.4, p = 0.97) for patients receiving 1-3 injections, 14.9 (13.7-16.1, p = 0.96) for 4-6 injections, 14.8 (12.4-17.2, p = 0.84) for 7-9 injections, and 15.7 (14.0-17.4, p=0.56) for 10+ injections.

Conclusion: There was no statistically significant increase in IOP over time for AMD or DME patients, regardless of the number injections received. Ours is the only study we are aware of to track the progression of IOP over a period of greater than two years and to stratify by number of injections received. It is notable that neither of these variables affected IOP, as they have been proposed as potential factors contributing to increased IOP after injections.

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Post-discharge Falls and Readmissions: Associations with Insufficient Vision and Low Health Literacy among Hospitalized Seniors

Ethan Jaffee

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Co-Authors: Vineet Arora, MD, MAPP; Madeleine I. Matthiesen, MD; Seenu Hariprasad, MD; David O. Meltzer, MD, PhD; Valerie Press, MD, MPH

Background: The role of patient-level risk factors such as insufficient vision has been under-studied. Because insufficient vision may interfere with health literacy assessments, the full impact of low health literacy among older patients with impaired vision is unknown. We sought to determine whether senior inpatients' insufficient vision and low health literacy are associated with adverse outcomes post-discharge, specifically falls and readmissions.

Methods: We conducted an observational study of adult medicine inpatients at an urban hospital. Visual acuity and health literacy were screened at bedside. Outcomes data were collected by telephone 30 days post-discharge.

Results: Among 1,900 participants, 1,244 (65%) were reached post-discharge; 44% had insufficient vision and 43% had low health literacy. Insufficient vision was associated with post-discharge falls among participants >65 years (adjusted odds ratio [AOR] 3.38, 95% confidence interval [CI] 1.42-8.05), but not among participants <65 years (AOR 1.44, 95% CI 0.89-2.32). Low health literacy was associated with readmissions among participants >65 years (AOR 3.15, 95% CI 1.77-5.61), but not among participants <65 years (AOR 0.78, 95% CI 0.56-1.09).

Conclusion: The results suggest the need to implement screening for older inpatients' vision and health literacy. Developing effective interventions to reduce these risks is critical given national priorities to reduce falls and readmissions.

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Using the Hospital Setting to Identify and Improve Vision Needs of Inpatients with Diabetes

Allison Louis

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Background: Patients with diabetes are at higher risk for medical eye disease and yearly dilated eye exams are recommended. However, gaps in preventative care occur, particularly among underserved minority patients. To reduce health disparities, the hospital setting may be an opportunity to connect patients to vision care. Our objective was to identify vision care needs of inpatients with diabetes and assess the feasibility of using the hospital setting to facilitate post-discharge care.

Methods: Research assistants (RAs) at the University of Chicago Medicine enrolled inpatients who were ≥18 years, English-speaking, and cognitively intact. The Visual Function Questionnaire (VFQ) was administered to assess vision related quality of life and participants had their vision screened. Those with vision >20/40 in both eyes and not wearing corrective lenses were given non-prescription readers and re-screened to determine if vision could be corrected. Participants with diabetes were identified by medical record and self-report. A subset of participants were given readers to take home. RAs called participants 30 days after discharge to re-administer the VFQ and obtain information regarding follow-up care. Means were compared using t-tests and categorical comparisons used Chi-square.

Results: 225 inpatients had vision screened. 20% had diabetes, 50% were female, 83% were African American, and the mean age was 54 years. 30% (14/46) of participants with diabetes had sufficient vision; 32% (15/46) had insufficient vision but were wearing corrective lenses; and the remaining participants had insufficient vision and did not have corrective lenses (37%, 17/46). All participants without lenses (n=17) had vision re-screened using readers; 2/3 had their vision corrected (11/17), and 53% (9/17) went home with readers. 49% of participants with diabetes reported seeing an eye doctor yearly. During hospitalization, over 3/4 (176/225) of the total study population completed the VFQ. The VFQ was lower for participants with diabetes (n=37) versus those without diabetes (n=139; mean score of 83 versus 88; p<0.05). There are no significant findings at 30-day follow-up. Almost 3/4 of inpatients with diabetes agreed that they needed to see an eye doctor and 89% (41/46) reported they would likely see one if advised by a provider. On 30-day follow-up, 55% (6/11) endorsed that they need to see an eye doctor, however only 36% (4/11) had scheduled an appointment.

Conclusion: Our study demonstrates inadequate vision is prevalent among inpatients with diabetes. 1/3 had insufficient vision without corrective lenses, of whom 2/3 had their vision corrected by readers. The hospital setting is an important opportunity to provide vision screening and intervention because it is a transition point in care and relies heavily upon written materials. While only 1/3 of participants scheduled an appointment with an eye doctor upon 30 day follow-up, all agreed that they would likely see one if advised by a provider, demonstrating the importance providers play in preventative care of patients.

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Associations Between Childhood Trauma And Impulsivity
Catherine Trippe

Mentor: Harriet de Wit, PhD, Department of Psychiatry and Behavioral Neuroscience

Co-Authors: Jessica Weafer, PhD; Harriet de Wit, PhD

Background: Impulsive behavior is symptomatic of many serious psychiatric disorders, including drug abuse, and it is therefore important to study the development of impulsivity. Childhood trauma and impulsivity have been positively correlated in various populations with psychiatric diseases such as depression, eating disorders, and substance dependence. However, fewer studies have examined this relationship in healthy populations. Further, little is known about the genetic underpinnings of this association.

Methods: Over 1,200 healthy volunteers aged 18-30 were recruited from the community surrounding the University of Chicago and University of Georgia. Childhood trauma was assessed using the Childhood Trauma Questionnaire. Impulsive choice was assessed using a delay discounting task to measure the perceived value of immediate versus delayed rewards. Impulsive personality was measured using the Barratt Impulsiveness Scale-11. Genetic analyses yielding a number of Small Nucleotide Polymorphisms (SNPs) were performed using saliva sampling. A literature search was conducted identifying four SNPs likely to interact with trauma to affect delay discounting. ANCOVA using Age, Sex, and income as co-variates was performed to search for interaction effects between trauma and SNPs.

Results: Approximately 20% of respondents had experienced some type of childhood trauma. The most common type of childhood trauma was Emotional Neglect (10.4%), and the rarest was sexual abuse (5.5%). Demographics were generally similar between groups. Subjects who experienced emotional/sexual abuse and physical neglect showed significantly greater delay discounting. Greater impulsive personality was seen in subjects with physical/emotional abuse, physical neglect and multiple trauma types. Specific factors of impulsive personality were associated with different trauma types. Only two SNPs occurred in Hardy-Weinberg equilibrium and could be analyzed for gene-trauma interaction effects. Of these, the most significant interaction seen was a COMT SNP with physical abuse in ANCOVA (p=0.040, effect size = 0.32%).

Conclusion: In our relatively healthy population, a significant minority experienced some form of childhood trauma. Of the types of childhood trauma studied, physical abuse likely has the most association with greater delay discounting. Impulsive personality traits are likely influenced by multiple types of trauma. SNPs associated with the processing of serotonin and dopamine may have a small effect on the processing of childhood trauma. In particular, a COMT SNP causing an Val158Met transition which results in higher COMT activity and therefore lower dopamine levels may increase resiliency and therefore affect the experience of childhood trauma. Our finding is preliminary and further analyses such as structural equations modeling could help to confirm this hypothesis. Despite the many limitations of this study, such as the retrospective trauma measurement and the relatively homogeneous population, this study represents an initial attempt to parse out the multi-factorial effects of genetics and childhood trauma on impulsivity.

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Adherence to National Comprehensive Cancer Network Guidelines for Testicular Cancer

Kevin Wymer

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Co-Authors: Shane Pearce, MD; Kelly T. Harris, MD; Phillip M. Pierorazio, MD; Siamak Daneshmand, MD; Scott Eggener, MD

Background: Testicular cancer is the most common malignancy among young men and well established treatment guidelines exist to optimize outcomes. We characterized errors in the management of testicular cancer observed among patients seen at three referral centers in the United States.

Methods: We retrospectively reviewed data from 593 patients presenting with testicular cancer to three academic medical centers from 2007-2016. Non-guideline directed care (NGDC) was defined as management differing from National Comprehensive Care Network (NCCN) Guideline recommendations. Cases of NGDC were systematically described. Patient and tumor characteristics were compared between guideline directed care (GDC) and NGDC. Multivariable logistic regression was used to identify predictors of NGDC and Cox regression modeling was used to assess the association between NGDC and relapse-free survival.

Results: NGDC was identified in 177/593 (30%) patients. Inappropriate imaging (44%) and overtreatment (40%) were the most common. Misdiagnosis (24%) and undertreatment (16%) were relatively frequent, while inappropriate treatment (6%) was rare. On multivariable analysis, risk factors for NGDC included metastatic disease (OR= 2.17, p<0.01), presentation with testicular pain (OR= 1.89, p=0.02) or metastatic symptoms (OR= 4.60, p<0.01), and diagnosis at a low-volume center (OR=3.46, p<0.01). Undertreatment was found to be a significant predictor of disease relapse (HR=3.36, p<0.01).

Conclusion: NGDC of patients with testicular cancer is common, most frequently inappropriate imaging and overtreatment. NGDC leads to delayed definitive therapy, unnecessary morbidity, and higher rates of relapse. Risk factors for NGDC include metastatic disease, presentation with testicular pain, symptoms from metastases, and diagnosis at a low volume center.

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