
*75th Annual
Soma Weiss
Medical and Dental*

Student Research Day

January 15, 2015



Book of Abstracts

HARVARD MEDICAL SCHOOL
Scholars in Medicine Office

The Soma Weiss Student Research Day

This day honors the memory of Soma Weiss, MD (1899-1942), an inspiring teacher and physician at HMS and an ardent supporter of student research. Soma Weiss was born January 27, 1899 in Besterce, then a part of Hungary. He immigrated to New York in 1920 and graduated from Cornell Medical College in 1923.

Soma Weiss came to Harvard Medical School in 1925 when he was appointed assistant at the Thorndike Memorial Laboratory and Research Fellow in the Department of Medicine. He rose rapidly, demonstrating his great ability as an investigator, teacher, administrator, and clinician. Within four years, Dr. Weiss was appointed Assistant Professor of Medicine. His medical capabilities, his diplomatic handling of difficult situations, and his amicable personality led to his appointment as Director of the Second and Fourth Medical Services at Boston City Hospital in 1932. In this position, he took charge of the fourth year medical students, winning their admiration and affection. One of the important contributions he made to teaching was in his development of the Clinico-Pathological Conference at the City Hospital. His own bi-weekly Pharmacological-Therapeutic Conference gave the students unusual insight into the use of drugs.

Soma Weiss possessed all the qualifications necessary for the great clinician. He was a master of observation. His ward rounds were excellent; while conducting them, he never neglected the patients, the students, or the visiting physicians. He kept them all in proper balance while he dominated the whole. He wisely insisted that clinical work must be the basis for the study of disease.

Soma Weiss became the second Physician-in-chief of the Peter Bent Brigham Hospital in 1939. He died January 31, 1942 from the rupture of a congenital intracranial aneurysm. In the intervening years, his generous spirit, his eager and able services for the Hospital, his great abilities as a physician, investigator, and teacher, left an indelible imprint on the many students he mentored.

Harvard Medical School wishes to thank the Weiss family for their generous support of the Annual Soma Weiss Student Research Day.

Soma Weiss
1899-1942



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HARVARD MEDICAL SCHOOL

75TH ANNUAL

Soma Weiss
Student Research Day
January 15, 2015

Poster Sessions

1:00 - 3:00 PM

Atrium of the Tosteson Medical Education Center
260 Longwood Avenue, Boston, Massachusetts

Student Presentations

3:15-4:15 PM

Tosteson Medical Education Center, second floor

Reception and Poster awards

4:15 – 5:40 PM

Atrium of the Tosteson Medical Education Center

History of Soma Weiss Day

Jeffrey Flier, MD, *Dean of the Faculty of Medicine and Caroline Shields Walker Professor of Medicine at Harvard Medical School*

Robert Weiss, *Son of Soma Weiss, CBS Boston travel contributor*

Introductions

Patricia D'Amore, PhD, *Charles L. Schepens Professor of Ophthalmology, Schepens Eye Research Institute, Massachusetts Eye and Ear; Chair, Faculty Committee on Scholarship in Medicine*

Student Speakers

Aaron Deutsch (London) -

Non-additive effects of HLA genes in five common autoimmune diseases

Pranoti Hiremath (Peabody) -Identifying early changes in myocardial microstructure in hypertensive heart disease

Bennett Lane (Holmes) -Association of head and neck surgical outcomes with surgeon and hospital financial incentives

Ivana Viani (Cannon) -Dr. Vesna Bosanac: Ethical decisions in times of war

Awarding of Poster Prizes

Elizabeth D. Hay Prize for Basic Science Research

Judah Folkman Prize for Clinical / Translational Science Research

Charles Janeway Prize for International Research or Service

Robert Ebert Prize for Health Care Delivery Research or Service

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**Gender Trends in Obstetrics and Gynecology Department-based Leadership Roles
across ACOG Districts**

Ashley Aluko

Harvard Medical School, Walter Bradford Cannon Society, Class of 2015

Hope Ricciotti, M.D.

Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center

The objective of this study was to determine whether the gender of department-based leaders in each American Congress of Obstetricians and Gynecologists (ACOG) district reflects the composition of its obstetrics and gynecology physician base.

We searched United States obstetrics and gynecology departmental websites for the gender of leaders (chairs, vice chairs, division directors, clerkship directors, residency directors and fellowship directors). The proportion of women obstetrician-gynecologists in each ACOG district was derived from 2013 AAMC data. We compared proportions of women leaders and women obstetrician-gynecologists within each district and calculated ratios of the proportions (1.0 indicates proportional representation of women leaders).

Half (50.2%) of active obstetrician-gynecologists in the United States were women. In each district the proportion of women leaders was lower than the proportion of women obstetrician-gynecologists; this discrepancy was statistically significant for all districts (all P less than 0.03) except VIII (Northwest/Southwest/West), IX (California) and XII (Florida). The ratio of women leaders to obstetrician-gynecologists was above 0.80 in District VI (Midwest), VIII and IX, but below 0.60 in District III (Mid-Atlantic) and VII (South). The ratio was below 0.80 for the chair role in all districts, with a low of 0.15 in District XI (Texas). The ratio was above 0.80 for the clerkship director role in all districts and residency director in all but three districts.

There was notable geographic variation in representation of women in department-based leadership roles relative to gender composition of the physician base. The proportion of women leaders was lower than the proportion of women obstetrician-gynecologists in every district. Women were more often underrepresented in administrative than educational roles. While the reasons for geographic variation are unknown, differences in geographic mobility, priorities, and publication rates between men and women over their career spans, in addition to subtle gender bias, could partly explain this complex finding.

mHealth Application Improves Medication Dosing Accuracy and Efficiency Among Junior Physicians in Guatemala**J Bradley Segal****Harvard Medical School, Walter Bradford Cannon Society, Class of 2017****Ben Arevalo****Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017****Daniel Palazuelos, MD, MPH****Department of Medicine, Division of Global Health Equity
Brigham and Women's Hospital**

More than half of the medical errors made by junior physicians are prescription mistakes, and more than half of these errors occur when a medication is dosed incorrectly. Here a cell phone-based electronic reference tool—an app—to help clinicians safely and efficiently dose medications was developed and then studied to assess the tool's dosing accuracy, timeliness, patient centeredness and usability.

The mHealth tool was programmed using CommCare HQ, incorporating standard dosing guidelines for eleven medications picked by our partner organization, Primeros Pasos. Primeros Pasos, located in Quetzaltenango, Guatemala, has rotating Guatemalan '*externos*'—equivalent to American interns—ranging in age from 21 to 24. Over six weeks six *externos* were given a smart-phone containing the app in a step-wedge study design. Dosing was monitored in real time to ensure the app suggested safe doses. Pharmacy records were analyzed, *externos* were timed during brief clinical encounters, patients were asked quality improvement survey questions, and *externos* answered quantitative and qualitative questions about their user experience.

With the app, patients were seen 27% faster ($n=275$, $p<0.000001$) on days when the clinicians were asked to see as many patients as they were able to in a limited time. On these days, clinicians using the app were 22% ($SD=6.3\%$) faster on average. Without the app medications were dosed incorrectly 34% ($n=142$) of the time. There was a net 43% ($p<0.0001$) improvement in dosing accuracy when medications were dosed using the app, raising total dosing accuracy to 94% ($n=216$). All of the clinicians testing the app had previous experience with smart phones and reported that the app was easy or very easy to use. No change in patient-centeredness was reported ($n=167$).

Overall, the app was demonstrated to be safe and efficient. Making this app available to junior physicians familiar with smartphones can improve patient safety by greatly enhancing dosing accuracy. The phone's significant improvement of provider timeliness is of particular utility in situations when providers need to see an overwhelming number of patients in a limited amount of time—a scenario in which dosing errors were more likely to occur. More medications can easily be added to the app to help clinicians in other locations with different needs. New strategies in introducing the technology to care providers could help improve provider trust in the app thereby making the app even more effective.

**Geriatric Bipolar Depression: An Open Label Study of Lamotrigine and
an Evaluation of Markers of Cerebral Energy**

Olusola J. Ayankola

**Harvard Medical School, Walter Bradford Cannon Society, Class of 2017
NIH-Funded Geriatric Psychiatry Summer Fellowship**

Dr. Brent Forester MD, MS

**Geriatric Psychiatry, Department of Psychiatry
McLean Hospital**

As the aging population around the world grows, heightened research efforts to better understand the impact of aging on psychiatric illness are imperative. Bipolar disorder (BD) is estimated to occur in 2.6% of the US adult population and 2.4 % of the world's population and has profound deleterious effects on quality of life for both patients and their caregivers. Although many clinicians maintain that earlier-onset bipolar disorder, "burns out" with aging, cross-sectional analyses have reported that older adults with BD continue to use health services at high rates. Furthermore, BD of late-onset, though rare, often follows a chronic and potentially fatal trajectory.

Bipolar depression remains the predominant phase of illness in later life and proves difficult to diagnose and treat. Further, we currently have a limited understanding of the pathophysiology of bipolar depression. Some studies suggest a defect in cerebral energy metabolism, specifically related to mitochondrial dysfunction. No studies have directly evaluated changes in cerebral energy metabolism in older adults with bipolar depression despite significant evidence that mitochondrial functioning worsens with the aging process alone. Effects of lamotrigine on the markers of cerebral energy metabolism have also not been studied in this population.

We performed a ¹H MRS study at a 4-Tesla magnetic field strength measuring energy metabolites in subjects with late-life BD versus normal comparison subjects. The following hypotheses were tested: 1) that the concentrations of glutamate and glutamine will be increased in late-life BD depression compared to normal elderly subjects, resulting in increased demands on neuronal energy metabolism; and 2) that patients with late-life BD depression will show an increase in lactate confirming findings that an increase in energy metabolism or mitochondrial dysfunction will result in a shift to glycolysis and pyruvate production; 3) that there will be a decrease in NAA reflecting the reduction in ATP production; 4) that the depression symptom severity score will correlate with concentrations of lactate, glutamate, glutamine and NAA; and 5) that treating patients with late-life BD depression for 8 weeks with lamotrigine will correct for aberrations in cerebral energy metabolism so that the metabolites more closely mirror healthy controls.

Does illicit drug use influence inpatient adverse events, death, length of stay and discharge after orthopaedic trauma?

Victor D. Babatunde

Harvard Medical School, Walter Bradford Cannon Society, Class of 2017

David Ring, MD, PhD

**Orthopaedic Hand and Upper Extremity Service,
Massachusetts General Hospital**

Illicit drugs are substances such as opiates (including prescription opioids), cocaine, cannabis, prescription psychotherapeutics used non-medically. The prevalence of illicit drug use in adults is increasing, but the risks of illicit drug use after orthopaedic trauma are not well studied. Our primary null hypothesis was that illicit drug use is not associated with inpatient adverse events after admission for musculoskeletal trauma. Secondary study questions addressed the association of illicit drug use with mortality, prolonged hospital stay, and nonroutine discharge.

Using the Nationwide Inpatient Sample (NIS) database, we identified an estimated 7,118,720 orthopedic trauma inpatients from 2002-2011 and separated them into 2 groups: illicit drug users (1.5%) and non-illicit illicit drug users (98.5%). Multivariable regression modeling was used to determine the association between illicit drug use and the each of the outcome variables.

Illicit drug use was associated with higher odds of inpatient adverse events (odds ratio [OR], 1.6; 95% confidence interval [CI], 1.6-1.7; $P<0.001$), lower likelihood of inpatient death (OR, 0.79; 95% CI, 0.72-0.88; $P<0.001$), prolonged hospital stay (OR, 1.4; 95% CI, 1.4-1.5; $P<0.001$) and higher odds of being discharged nonroutinely (OR, 1.3; 95% CI, 1.3-1.4; $P<0.001$).

A major limitation to our study was that the NIS database is an administrative dataset based on billing codes, which may only identify a subset of illicit drug users. Another limitation is that the NIS database does not allow us to determine if patients who were coded with the diagnosis of illicit drug use had active disorder, had been treated for this condition, or were actively on therapy around the time of surgery.

ICD-9 coding for illicit drug use in a large national database was associated with increased likelihood of inpatient medical adverse events, prolonged hospital stay, and nonroutine discharge after orthopaedic trauma. Prompt recognition and proactive treatment measures for patients who have a history of illicit drug use may inform the management of orthopedic trauma inpatients.

Parental interest in newborn genetic testing: a randomized, factorial survey**Danielle K. Bäck****Harvard Medical School, Francis Weld Peabody Society, Class of 2017****Robert C. Green, MD, MPH****Division of Genetics and Department of Medicine
Brigham and Women's Hospital and Harvard Medical School**

Previous studies have demonstrated high levels of parental interest in genetic newborn testing. However, researchers have not yet examined whether parental preferences for genetic newborn testing change over time or after being presented with hypothetical genetic test results. We hypothesized that parental preferences for genetic newborn testing are not associated with time of inquiry or the presentation of hypothetical genetic test results.

We randomized 1,096 parents in the Postpartum Unit at Brigham and Women's Hospital (mean age (sd) 32.4 (6.0) years, 65.2% female, 60.6% white) to be surveyed about their interest in hypothetical newborn genetic testing, either in hospital within 48 hours of birth or 3-24 months later. Demographics were collected for all participants during the baseline survey. Using a factorial design, these respondents underwent a second randomization at follow-up; 535 parents were randomized to a second survey that assessed interest in newborn genetic testing, parental stress, and parental behaviors, while 561 parents were randomized to a second survey that examined the previous measures, as well as parental interest in newborn genetic testing following a presentation of hypothetical genetic test results. Our follow-up rate is currently 60.6%.

Preliminary analysis with logistic regression found no difference in parental interest in genetic newborn testing between parents who were queried in hospital and those who were surveyed 3-24 months later (OR: 1.33, 95% CI: 0.88-2.02, $p=0.171$). Our analysis also found no difference in parental interest in genetic newborn testing among those who were presented with hypothetical genetic test results, compared to those who were not presented with these results (OR: 1.02, 95% CI: 0.68-1.54, $p=0.94$). Overall, parental interest in genetic newborn testing is high, as respondents reported being not at all (8.4%), a little (11.7%), somewhat (33.7%), very (27.8%) or extremely (18.4%) interested in genomic testing for their newborns.

These results suggest that regardless of when a survey was conducted or the amount of hypothetical information presented, parents of newborns have high levels of interest in genetic newborn testing. If genetic newborn testing is integrated into clinical practice, our research implies that parents are capable of making informed decisions about this testing in the early postpartum period without the complexity of presenting hypothetical results.

Opioid Prescribing Following the Extraction of Teeth

James Baker

Harvard School of Dental Medicine, William Bosworth Castle Society, Class of 2017

Jerry Avorn, MD and Brian Bateman, MD, MSc

**Division of Pharmacoepidemiology and Pharmacoeconomics, Department of
Medicine**

Brigham and Women's Hospital

Context: Pain medication overuse has become a major problem in the United States, and dentists may inadvertently play a role in this. Dentists commonly prescribe opioids to manage post-surgical pain following procedures such as extractions, and root canal procedures. Dental care has been associated with increased prescription drug availability in communities, and increased rates of abuse.

Objective: To characterize the opioid prescribing patterns of dentists and oral surgeons following the extraction of teeth.

Methods: We analyzed opioid prescription drug use in patients from the national Medicaid Analytic eXtract (MAX) who had teeth extracted in the years 2000 to 2006.

Results: The cohort from 2000-2006 included 3,669,635 patients who underwent dental extractions. Nearly a quarter (23.6%) of the cohort filled a prescription for at least one opioid. The most common prescriptions were for hydrocodone (75% of all opioid prescriptions), oxycodone (15%), propoxyphene (5%) and codeine (3%). Of the filled prescriptions in the entire cohort, the median dose in morphine equivalents was 105, which equates to 21 pills of 5 mg hydrocodone. There was also significant variation within the cohort, showing that prescribing practices are not uniform among dentists and oral surgeons. The interquartile range represented a span of 70 morphine equivalents, from 80 morphine equivalents (16 pills of 5 mg hydrocodone) in the lowest quartile to 150 morphine equivalents (30 pills of 5 mg hydrocodone) in the third quartile. For some of the more invasive procedures, the median dose reached 150 morphine equivalents, or 30 pills of 5 mg hydrocodone.

Conclusions: Many patients are prescribed large quantities of opioids following tooth extractions. This may represent an excess in prescribing, and a means for opioids to enter communities and thereby contribute to prescription drug abuse.

**Identifying Best Practices to Reduce Hospital Admission of Chest Pain from the
Emergency Department**

Alexis Ball

Harvard Medical School, William Bosworth Castle Society, Class of 2017

Dr. Jeremiah Schuur, MD, MHS

Department of Emergency

Medicine of the Brigham and Women's Hospital

Individuals presenting to the ED with chest pain accounts for roughly 5.8 million visits to per year in the United States. The decision to admit these patients to the hospital after an emergency department (ED) visit is one of the most costly actions that an emergency provider routinely takes; yet it is variable by provider and institution. Improving the efficiency of this process has the potential for significant savings since annual direct costs of patients admitted from the ED with a diagnosis of chest pain are approximately \$3.1 billion in the United States (8). We believe possible causes for variation include patient factors (acuity of illness, availability of PCP for outpatient follow up, etc.), physician factors (risk tolerance, quality of physician, etc.), and facility factors (culture and norms, etc) We aimed to identify strategies to facilitate discharge among EDs with low admission rates.

This project focused on one condition, chest pain, within the qualitative part of a larger mixed methods project. The first phase of the project used quantitative analysis of administrative data to prioritize three common diagnoses (chest pain, diverticulitis, and asthma), identify the most appropriate post ED critical pathways, and identify EDs in Massachusetts with low admission rates. A technical expert panel composed of 2 academic and 2 community-based ED physicians, a hospitalist, a primary care physician, a surgeon, a case manager, and representatives from an insurer, risk management and patient advocacy helped to characterize these parameters. In order to identify best practices of managing chest pain that are translatable to other EDs, we are utilizing qualitative techniques to explore barriers that hospitals with low ED admission rates have encountered, and identifying successful approaches for outpatient management. We have interviewed the ED directors at three EDs and interviewed care providers at several EDs (emergency physicians, case manager). The analysis of the interviews is ongoing. Initial findings of strategies that high-performing ED use include: availability of next day stress tests for patients with chest pain, availability of cardiology consultations in the ED, and sharing of performance data with physicians.

A Comparison of Endoscopic and Pi Craniectomies for Sagittal Craniosynostosis

Arthur R. Bartolozzi, MPhil
Harvard Medical School, Francis Weld Peabody Society, Class of 2017

Suresh N. Magge, MD
Department of Neurosurgery
Children's National Medical Center, Washington, DC

Craniosynostosis, or premature fusion of the cranial sutures, affects 1 in 2000 births, and sagittal craniosynostosis is the most common type. There is debate over best surgical intervention for this condition. Our aim was to compare two surgeries that are done at a young age: the open "Pi" craniectomy and the minimally-invasive endoscopic-assisted strip craniectomy followed by helmet therapy. In this study, we compared the effectiveness of these two techniques as well as the effect of insurance status, time to presentation, and outcome.

This was an IRB-approved, retrospective study which included 47 patients diagnosed with non-syndromic, single suture sagittal craniosynostosis who were treated at Children's National Medical Center with either pi craniectomy (n=24) or endoscopic strip craniectomy followed by helmet therapy (n=23). Patients were treated between 2009-2014. Further, patients were only included if they had documented follow-up appointments more than 150 days after their surgery. Statistical calculations including t-tests were completed using STATA 12.0 SE. Statistical significance was predetermined at $p < 0.05$.

Both groups started with statistically similar initial cranial measurements, but endoscopic patients experienced a 15.6% increase (from $CI=0.673$ to $CI=0.778$) over 1.23 years follow-up compared to pi patients' 5.1% increase (from $CI=0.685$ to $CI=0.720$) over 2.50 years ($p < 0.001$). Hospital stay (1.17 days, endoscopic; 1.96 days, pi) and operation duration (68 minutes, endoscopic; 93 minutes, pi) were both significantly shorter for endoscopic patients ($p < 0.001$). Pi patients had a significant change in their head circumference percentile while endoscopic patients did not. Increased age at initial presentation ($-2.15\% CI/month$, endoscopic; $-0.18\% CI/month$, pi) and at surgery ($-1.43\% CI/month$, endoscopic; $-0.39\% CI/month$, pi) resulted in worse outcomes for endoscopic patients. Medicaid or private insurance status did not correlate with either percent change in CI ($p=0.52$) or time to presentation ($p=0.80$).

Endoscopic-assisted strip craniectomy with molding helmet therapy showed superior results with respect to cranial index compared to Pi craniectomy. Younger age at time of surgery affected the outcomes of endoscopic surgery more than the outcomes of Pi craniectomies. Insurance status did not compromise access or care.

Bruxism and Enamel Erosion in Patients Treated with HIV Retroviral Therapy

Grace E. Beck

Harvard School of Dental Medicine, William Bosworth Castle Society, Class of 2017

Jay Anderson, DMD, MHSA

**Russell Street Community Dental Clinic, Department of Community Dentistry
Oregon Health and Science University**

Bruxism is a condition in which a person excessively grinds his or her teeth and/or clenches his or her jaw. If left untreated, bruxism can cause destruction of tooth structure, increased enamel erosion, damage to the temporomandibular joint, and severe headaches. Although certain medications are known to trigger bruxism, the relationship between HIV anti-retroviral therapy and bruxism has not been investigated in a clinical setting.

Oral health care providers at Russell Street Clinic, a non-profit community dental clinic in Portland, Oregon, have observed severe enamel erosion in patients who are treated with HIV retroviral medication. This increased enamel erosion and tooth wear is likely the result of bruxism that is induced by HIV anti-retroviral therapy. To elucidate the relationship between HIV anti-retroviral therapy and bruxism, an observational study was conducted at Russell Street Clinic.

A patient survey and clinical examination were used to compare the degree of bruxism and tooth wear in ~60 HIV positive and ~40 HIV negative individuals that consented to participate in the study. The patient survey inquired about each participant's gender, age, HIV status, current medications, awareness of tooth grinding or clenching jaw, gum, tooth soreness, and frequency of headaches. For the clinical evaluation, a dental provider recorded the degree of wear on each tooth using a scale of 1—3, 1 being wear through the enamel to the dentine in single spots and 3 being wear of the dentine more than one-third of the crown height. The data obtained from the patient survey and clinical evaluation will be analyzed to explore any differences in enamel erosion between HIV patients on anti-retroviral therapy and non-HIV patients. Further, we will conduct an ANOVA with age group as a factor and correct for potential confounding variables such as psychosocial or psychiatric disorders, alcohol intake etc.

Isolated Collateral Ligament Knee Injuries in Children: A Retrospective Review of the Pediatric Experience**Iman K. Berrahou****Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017****Dennis Kramer, MD****Department of Orthopedic Surgery, Boston Children's Hospital**

In the knee, the medial (MCL) and lateral (LCL) collateral ligaments and posterolateral corner (PLC) provide stability. Injuries to these ligaments can result in significant time lost to injury. The vast majority of research on MCL and LCL injuries has focused on concomitant anterior cruciate ligament injuries in the adult population. Research on isolated collateral ligament injuries in the pediatric population is sparse.

The purpose of our study was to determine patient and injury characteristics associated with isolated collateral ligament injuries in adolescents. Secondary aims included determining the time to return to sports (RTS) and identifying risk factors for prolonged RTS, reinjury, and continued pain in this population. We hypothesized that patients with higher grade injuries have a longer RTS time and increased risk of continued pain and reinjury.

We queried the Boston Children's Hospital Department of Orthopedics database to identify all patients under age 18 who sustained an MRI-confirmed isolated complete or partial MCL or LCL tear or PLC injury between January 2005 and December 2012 (n=60). Patients with associated ACL tears were excluded. Charts and MRIs were reviewed to document patient and injury characteristics. Statistical analysis was done to analyze risk factors for prolonged RTS, continued pain or reinjury.

Sixty patients (38, 63% male), mean age 14.4 range (5-19), were identified, of which 48 (80%) had MCL injuries. Twelve (20%) had LCL injuries with four (7%) concurrent PLC injuries. Forty-nine (82%) patients had injuries that occurred during sports. Univariable analysis determined that patients whose injury occurred during sports had a shorter recovery time (sport injury: mean \pm SD, 2.2 \pm 1.2 months; non-sport injury: 3.0 \pm 0.8 months; $p=0.01$). Nine (15%) experienced a reinjury, fourteen (23%) were followed for continued pain, and twelve (20%) had patellar instability. Football injuries were more likely to be grade 3 ($p=0.02$), and football and soccer accounted for all grade 3 injuries. Subjects who were injured on grass had nearly four times the odds of a higher grade injury (OR=3.73; 95%CI= (1.2-11.8); $p=0.02$). Patients with history of a prior injury had 80% lower odds of a higher grade injury (OR=0.20; 95%CI= (0.05-0.86); $p=0.03$).

Study limitations include short follow-up as most patients returned to sports without complication.

This data provides patients and injury characteristics for adolescent patients who sustained a physician-diagnosed, MRI-confirmed isolated collateral ligament injury. Football and soccer were associated with the highest grade injuries, while patients with a history of prior injury were more likely to have low-grade injuries. Patellar subluxation is a common associated injury.

**Predictors of Patient Reported Outcomes of Total Joint Arthroplasty in a
Developing Country**

Jennifer Bido

Harvard Medical School, Walter Bradford Cannon Society, Class of 2017

Jeffrey N. Katz, MD, MSc

**Orthopedic and Arthritis Center for Outcomes Research
Brigham and Women's Hospital**

The prevalence of osteoarthritis, one of the leading causes of global disability, is on the rise in developing countries due to an increase in the longevity of their citizens and the increasing prevalence of obesity. In response to the growing burden of joint disease, developing countries are creating their own total joint arthroplasty (TJA) programs for patients with severe OA as TJA is the most common and successful surgical intervention used in the developed world for pain relief and functional improvement. Current TJA research has focused on the use of patient-reported outcomes (PRO) to predict which patients are more likely to succeed. This work may be of particular importance to developing countries that have to determine how to best allocate their limited resources.

Although a significant amount of PRO research has been done to determine which patients are most likely to benefit from TJA, this work has only been done in developed nations. This investigation uses PRO data collected by a short-term medical mission, Operation Walk Boston, to the Dominican Republic to assess predictors of TJR outcome in a developing country.

We obtained information on 156 TJA patients from the Operation Walk Boston database. PRO data were determined from validated surveys, while demographics and medical details were abstracted from clinical notes. Using multivariable linear regression we were able to create models that assessed which preoperative factors were predictive of post-operative pain and function at one-year follow-up.

Our cohort had a mean age of 61.3 years and was mostly females (82%) who received knee replacements (79%). Males, patients with OA, and those with higher preoperative function had both better follow-up pain and function ($p < 0.05$ for all). High optimism (that outcome would be successful), younger age, and the use of a bilateral procedure were predictive of better functional outcome, though not of pain relief. Additionally, high preoperative pain was associated with a better follow-up pain than those who started at a low level of pain. Education level, BMI, number of co-morbidities and whether a total hip or knee replacement was performed were not predictive of any of the outcomes.

This data demonstrated that several factors were associated with successful TJA outcomes in a developing country. As two factors are modifiable, preoperative function and optimism level, efforts to improve outcomes should target these aspects. More research is needed to further elucidate how these patterns differ from those seen in developed countries.

**Bucharest Early Intervention Project (BEIP) Early Adolescent Follow-Up:
Intervention and Caregiver Effects on Long-Term Outcomes**

Simona Bor

Harvard Medical School, William Bosworth Castle Society, Class of 2017

Charles A. Nelson, PhD

**Neurobiology Program, Developmental Medicine Research Center
Boston Children's Hospital**

The Bucharest Early Intervention Project (BEIP) is the largest ongoing investigation of the effects of foster care placement on the cognitive development of children who were abandoned in Romanian institutions. Thus far, foster care placement has appeared to be beneficial for infants adopted from these institutions before they reached 2 years of age. In an effort to evaluate the long-term effects of the foster care intervention, follow up studies were conducted with the children and parents involved in the project through 12 years of age. The purpose of this project was to evaluate "This is My Child" interviews conducted on parents of children involved in the BEIP 12 years after it began; the "This Is My Child Interview" is a semi-structured interview that measures a parents' level of commitment, acceptance and degree of influence and was used to determine if parental/caregiver commitment mediates the effect of early placement on outcomes. Preliminary data suggests that while both biological and foster parents expressed strong levels of commitment and acceptance towards their children, foster parents expressed a greater degree of influence. Further research is warranted to elucidate the correlations between other factors, ranging from the number of children in the household to the number of years children spent in a given household, and the parameters measured by the "This is My Child Interview."

Can Mobile Clinics Improve Healthcare?**Zoe M. Bouchelle****Harvard Medical School, Francis Weld Peabody Society, Class of 2017****Nancy E. Oriol, MD****Dean for Students, Harvard Medical School**

There are an estimated 2,000 mobile health clinics operating in the U.S., receiving 6.5 million visitors annually. While researchers have established that mobile clinics achieve good patient outcomes, boast impressive returns on investment, and succeed in reaching vulnerable populations, there is relatively limited research examining why mobile clinics work from the patients' perspective. Knowledge of how mobile clinics are utilized to improve patients' personal healthcare landscape can yield insights into where traditional healthcare falls short, and how mobile clinics and other healthcare providers can work together to improve patients' health. The objective of this project is to characterize how patients use The Family Van, a Boston-based MHC, to improve their personal healthcare systems.

A qualitative design was chosen to explore clients' experiences receiving mobile and traditional health services. Data were gathered from semi-structured interviews with 25 patients receiving care on The Family Van from June-July 2014. Convenience quota sampling ensured representation of the following baseline characteristics: Male/female, White/Non-White, ≥ 65 / < 65 years of age, and Insured/Uninsured. Interviews were audio-taped, transcribed, and analyzed using a grounded theory approach. Strategies to ensure reliability include multiple coding rounds, iterative codebook development, and inter-rater reliability measurements. Limitations include a small, self-selected sample.

Data revealed three ways in which patients utilize The Van to improve their healthcare: 1) As a substitute to the traditional healthcare system, 2) As a supplement to the traditional healthcare system, and 3) As a link to the traditional healthcare system and social services. The perceived gaps in the traditional healthcare system that The Family Van fills include: 1) A lack of fast, affordable services to address minor health concerns, 2) Insufficient management and infrequent tracking of chronic disease, and 3) Sparse care addressing the social determinants of health.

This study joins a small but consistent body of literature indicating that mobile clinics facilitate access to healthcare. That most clients are insured is evidence that cost and lack of insurance are not the only factors promoting client attendance. These data suggest that clients are utilizing The Van to address gaps in the broader healthcare system that are encountered by all patients, not only those in underserved communities. Mobile clinics have the potential to work alongside traditional healthcare providers to assist in triage, disease management, prevention, and social services provision for all patients, regardless of race/ethnicity, insurance coverage, or socioeconomic status.

Male Perceptions of Obstacles to and Quality of Maternal Health Care in Kisumu County Kenya

Kathryn Brubaker

Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Roy Ahn, PhD

**Division of Global Health and Human Rights
Massachusetts General Hospital**

In 2009, Kenya experienced a maternal mortality rate of 488 deaths per 100,000 live births; only 47% of women received all four recommended antenatal clinic visits and only 44% had a skilled attendant at their birth. Despite the Kenyan government's recent policy decision to provide maternal care free of charge at public hospitals, preparing for and accessing that care at the time of delivery requires resources. Given the control that men have over family decision making and resource allocation in Kenya's patriarchal society and the extent to which they have typically been excluded from research on reproductive and maternal health in the past, it is important to understand their perceptions of the importance and quality of maternal health care.

In order to understand these attitudes, we carried out 18 focus groups in Kisumu County Kenya. Focus groups of women who had recently given birth focused on the obstacles they faced in accessing a skilled health facility and the role that their partner played in their delivery. Focus groups with community health workers explored the experience that they had had in engaging men in these topics. Finally, the focus groups with men themselves explored their knowledge of maternal health risks, experiences with maternal health care, and ideas of the major obstacles to access. The focus groups were carried out in both English and Luo. Focus group participants were recruited by a community health worker who had worked extensively throughout the county on issues of reproductive health and was able to target communities that were known to have challenges with access.

While I plan to complete the in-depth analysis and coding of the data this fall, preliminary analyses of the data highlight several themes. In every focus group, participants emphasized the problem that the cost of transportation and poor infrastructure posed. Many men said that they wanted to play a supportive role and provide for their wives care during delivery but that poverty made it difficult to do so. Community health workers highlighted the large improvements that had been made in community knowledge of safe sexual health practices since the advent of the AIDS crisis and were hopeful that a similar emphasis could be placed on safe maternal care.

The main limitation this study faced was difficulty recruiting male participants who were not invested in the healthcare system. While snowball sampling allowed us to talk to many people, not everyone agreed to participate.

Global Health Training in Infectious Disease Fellowship Programs**Agatha Brzezinski****Harvard Medical School, Walter Bradford Cannon Society, Class of 2017****Roy Ahn, MPH, ScD****Division of Global Health and Human Rights, Department of Emergency Medicine
Massachusetts General Hospital**

Interest in global health among physicians in training has been rising over the past 20 years. Recent publications document global health training among residency programs, but no comparable studies have yet been published for fellowship programs. Because infectious diseases continue to account for a significant portion of global mortality, it is important that physicians, especially infectious disease specialists, are trained in this area. Prospective fellows should take into account the global health offerings of a program when applying so as to maximize exposure to these opportunities. This study aims to assess the global health training that infectious disease fellowships offer by examining the curricula and the type of training programs available within these fellowships.

This is a cross-sectional review of global health training within infectious disease fellowships. Directors of all 143 ACGME-accredited infectious disease fellowship programs in the United States and Puerto Rico identified by the Infectious Diseases Society of America are surveyed to determine the type of global health training offered by programs. The survey measures the number, location, and duration of global health electives offered within programs, as well as the ease with which fellows participate, including whether programs incorporate orientations and post-elective debriefings. In addition, the survey seeks to assess interest and motivations in these programs, participation funding, mentorship in global health, and the value of these electives to the communities served and to fellows' development as infectious disease physicians. Finally, the survey also measures where and in what context fellows practice after fellowship completion.

Fellowship directors were invited via e-mail to participate in the online survey with follow-up reminders every two weeks to all directors who have not yet completed the survey and contact by phone after three reminders. If contact has not been made in eight weeks since the initial invitation, it will be assumed that the director in question does not wish to participate. The survey has been released and data is currently being collated. Data will be provided and analyzed in aggregate in Excel using univariate statistics. Important limitations include the survey design and response bias of fellowship directors of programs with a focus on global health. To minimize the effects of this limitation, nonresponders will be contacted regularly to target a response rate of 80%. Findings from this survey may be useful in directing the future focus on education and training in the field of infectious disease global health.

Anthropometric Analysis of the Female and Male Malay Nose**Ana Fernanda Calles****Harvard School of Dental Medicine, Oliver Wendell Holmes Society, Class of 2017****David Ngeow, DMD****Department of Oral & Maxillofacial Surgery
University of Malaya Hospital**

Anthropometry is the study of the measurement of the human body. Leslie G. Farkas pioneered modern anthropometry in a study that detailed the facial morphology of 26 ethnic groups. Farkas proved that varying degrees of differences in the size, shape, and proportions of facial structures exist among different ethnic groups; these differences are further stratified by gender. Recent clinical studies have measured, established, and compared the normative nasal measurements among African-American, Korean-American, Latino, Turkish, and Japanese ethnic groups. However, limited research has been conducted on the Malay population. This study aimed to expand facial anthropometric research to create normative nasal databases for this population and address a lack of specific anthropometric studies. It was hypothesized that there would be statistically significant differences between the male and female Malay nasal measurements. Furthermore, statistically significant differences were also expected when parameters were compared to that of other ethnic groups.

A no touch technique was used to characterize the craniofacial anthropometry of 100 Malay subjects. The subjects were recruited from the oral and maxillofacial surgery clinics of the University of Malaya in Kuala Lumpur, Malaysia. Specific inclusion criteria were followed and each subject was consented with Institutional Review Board approval from the Harvard Medical School and the University of Malaya. Ethnic background was determined and only pure Malay subjects were enrolled in the study. Images of each patient were obtained using a Vectra-3D FACIAL camera. The 3D photographs were then analyzed using mirror software to determine the measurements of several nasal landmarks.

SPSS was used to determine if the differences between the two groups (Malay Female, Malay Male) were statistically significant ($p < .05$). A statistically significant difference between both groups is expected. The averages will then be used to create 3D stereo models that will allow Southeast Asian plastic reconstructive surgeons, head and neck surgeons, oral and maxillofacial surgeons, orthodontists, and other practitioners to have baseline templates for the craniofacial complex of the Malays

**Development of oral health indicator survey to evaluate oral health status in
Ecuadorian children 6 and under**

Andrew Carranco

Harvard School of Dental Medicine, Oliver Wendell Holmes Society, Class of 2017

**Brittany Seymour, DDS, MPH
Harvard School of Dental Medicine**

In the first years of her Ecuador project, Dr. Sokal-Gutierrez and her team identified 88 percent of children under the age of 6 with dental caries. Ecuador contained some of the worse oral disease states documented by her and her team when compared to the other Latin American countries Dr. Sokal-Gutierrez has worked in. Despite the evidence of the identified trouble of oral diseases at the global level, several developing and emerging countries have yet to develop the routine oral health data collection needed for its country to properly characterize oral health status of its population.

An interdisciplinary team of researchers from Harvard University, Universidad San Francisco de Quito Dental School (USFQ), and UC Berkley have worked together to pilot an indicator survey to properly identify the oral health status of communities in Ecuador. An accurate health indicator survey will allow for more comprehensive decision-making at the policy level for oral disease intervention. With such oral indicators, an accurate and efficient process can therefore be used in oral health data collection as part of regular demographic health surveys and potentially further implemented globally.

Our indicator tool is composed of a previously designed survey with vigorous review of nutritional daily intake, current oral pain, activity level, and oral health understanding. The indicator survey was administered to 17 local communities of Pueblo Kichwa and Pambamarca Ecuador. In total we collected survey information from approximately 850 school-aged children. Oral screenings for caries, periodontal disease, and edentulism was also conducted on all participating children.

Currently, we are still in the stages of data input. We have approximately 100 children who have yet to be entered into excel data base with properly coded responses. Once all the participants have been entered, we will be doing a correlation analysis of particular question from the survey as they compare to the oral health of the child. Although complete analysis has yet to be finished there does seem to be correlative questions to the severity of oral disease. As predicted, there seems to be a trend of mouth pain associated with more severe oral health disease and diet dependent questions with primary and recurrent caries. Ultimately, we hope to create a cocktail of three or four questions from the indicator survey that accurately represent the oral health status of children in this age group.

Asian Americans and Prostate Cancer: A Nationwide Population-Based Analysis**Grace F. Chao****Harvard Medical School, William Bosworth Castle Society, Class of 2017****Michael O'Leary, MD and Quoc-Dien Trinh, MD****Division of Urology****Brigham and Women's Hospital, Harvard Medical School**

Asian Americans are the only racial group in which cancer is the leading cause of death. Prostate cancer (PCa) is the most common malignancy in men for nearly all Asian American groups. Despite the fact that "Asian American" is an extremely heterogeneous group, research literature generally examines all these groups as one. Disaggregation of Asian American data into the different ethnic groups is an important task few researchers have undertaken. It remains largely unknown if there are racial disparities in PCa in Asian Americans. Based on evidence of heterogeneity in PCa incidence within Asian Americans, we hypothesized heterogeneity in other aspects of the cancer profile: diagnosis, management, and survival relative to their Non-Hispanic White counterparts.

891,100 patients diagnosed between 1988 and 2011 within the Surveillance, Epidemiology and End Results (SEER) database were included. Patients were stratified according to ethnic group: Chinese, Japanese, Filipino, Hawaiian, Korean, Vietnamese, Asian Indian/Pakistani, Pacific Islander, and Other Asian. The impact of ethnic group on stage at presentation, rates of definitive treatment, and prostate cancer-specific mortality (PCSM) was assessed.

In adjusted analyses, Hawaiian men were more likely to present with metastatic disease (OR 1.698, 95% CI 1.411-2.043), to receive treatment for localized PCa (OR 1.635, 95% CI 1.337-2.000), and to be at risk for PCa death (HR 1.518; 95% CI, 1.304-1.766) than Non-Hispanic Whites. All had $p < .0001$. Filipino men were less likely to receive definitive treatment (OR 0.905, 95% CI 0.844-0.970, $p = .005$). Pacific Islanders (HR 1.425, 95% CI 1.119-1.816, $p = .004$) had increased risk of PCSM.

Limitations to the study include possible misclassifications of Asian Americans in the SEER database due to some classification based on birthplace and surname. Designation of men as "other Asian; Asian, not otherwise specified" precluded their statistical analyses as part of an ethnic group. Our study also did not account for Asian Americans of multiple races unless primary race in SEER was Asian.

Despite these potential limitations, our study highlights important ethnic differences in severity at presentation, definitive treatment, and cancer-specific mortality. Most Asian American groups were more likely to present with metastatic PCa compared with Non-Hispanic Whites. Notably, Hawaiians and Pacific Islanders were at greater risk for PCSM. Given the different cancer profiles, our results reveal a need for disaggregation of Asian American data. Targeted interventions to address different concerns of each group will allow for better health outcomes and more efficient use of healthcare resources.

**A Retrospective Cohort Study: Severe Early Childhood Caries Risk Associated with
Non-Fluoridated Toothpaste Use and Juice Consumption**

Michael Chen

Harvard School of Dental Medicine, Francis Weld Peabody Society, Class of 2017

Zameera Fida, DMD

**Department of Oral and Developmental Biology
Harvard School of Dental Medicine**

Early childhood caries cannot be eliminated through restoration or selected tooth extraction, and children afflicted with early childhood caries are more prone to dental caries in their permanent dentition. Management of infant oral health and prevention of early childhood caries constitute critical components of oral health beyond infancy.

Historically, over-the-counter fluoride toothpaste labels instructed consumers to ask a dentist for advice regarding use for children under 2 years of age. Recently the American Dental Association changed their guidelines on fluoride toothpaste use to include children of all ages. However, there is no fluoridated toothpaste formulated for use specifically for infants and toddlers in the United States, and non-fluoridated toothpaste is often used to avoid signs and symptoms of fluoride toxicity. Therefore, many parents may make their own decision on whether or not to use a fluoridated toothpaste.

Dental caries is a bacterially based disease that progresses when acid produced by bacterial action from dietary fermentable carbohydrates diffuses into the tooth and dissolves the mineral, that is, demineralization. In many tooth surfaces there will be very early stages of decay, and preventive agents such as fluoride (present in toothpaste or water) can act on subclinical and visible enamel decay to prevent progression to established decay. Dietary changes that reduce the frequency of simple carbohydrate consumption from juices might be an effective way to prevent severe-early childhood caries (S-ECC).

A retrospective chart review was conducted comparing children under age three without caries seen at Boston Children's Hospital (BCH) Department of Dentistry with children under age three with S-ECC seen at the BCH Lexington satellite facility operating room over a two-year span. Data was pulled from their first visit to determine a correlation between fluoridated toothpaste use, amount of daily juice consumption, and development of S-ECC. If such a correlation is determined to exist between toothpaste use and/or juice consumption, there would be implications for pediatric oral hygiene and dietary habits under the age of three.

Collaboration with a statistician is currently being performed to determine the results of the study. Caries is a multi-factorial process and as such, there will be confounding factors such as food intake. Responses from patients' parents may be subject to recall bias and/or skewed by imperfect perception, for instance, of juice intake.

Caregivers' Perspectives on Preschool Children's Beverage Consumption Behaviors and Influences

Cherry Choy

Harvard School of Dental Medicine, Francis Weld Peabody Society, Class of 2017

Inyang Isong, MD, MPH

Department of Medicine, Boston Children's Hospital

Background: Early childhood caries and obesity are two of the most prevalent chronic diseases affecting young children in the United States. While childhood caries and obesity are largely preventable through healthy dietary and lifestyle habits, many children continue to suffer from these diseases and their myriad consequences. Obesity and caries are associated with the development or worsening of several diseases, including: diabetes, cardiovascular diseases, and dyslipidemia.

Sugar sweetened beverages (SSB) are the largest source of beverage calories among children, and consumption of SSB is a known risk factor for caries and obesity in early childhood. While the largest increase in caloric contributions from SSB occur between ages 6-11 years, children's dietary and beverage consumption behaviors are known to develop at younger ages.

Study Aim: The goal of our study was to identify multi-level factors contributing to SSB consumption among preschool-aged children.. We also sought to elicit parents' preferences on how health care providers should deliver dietary counseling to reduce children's SSB consumption.

Methods: We employed a mixed qualitative and quantitative approach, using constructs from the Theory of Planned Behavior and Social Cognitive Theory to develop as our conceptual framework. We assessed parents' perspectives of multi-level determinants of preschool-aged children's beverage consumption, as well as strategies for translating this knowledge into positive dietary and oral health behavioral practices. We recruited 37 parents of preschool children ages 1-5years from clinics and early childhood community programs in Boston. Parent participants completed a survey that elicited beverage consumption habits of the parents and children, their perspectives on SSB's role in childhood caries and obesity, as well as additional socio-demographic information. We conducted 6 semi-structured interviews and 4 focus groups to explore in-depth, parent's perception on factors that contributed to their child's beverage consumption, possible health and social consequences of excess SSB consumption, and strategies employed by parents and medical professionals to promote healthier beverage consumption in young children.

Results: We are currently in the process of systematically coding all the transcripts from our interviews and focus groups using the online qualitative analysis software, Dedoose. After analysis, we will identify key themes, refine our conceptual framework report our results and conclusion.

Stratification of Recanalization for Patients with Endovascular Treatment of Intracranial Aneurysms**Michelle Chua****Harvard Medical School, Francis Weld Peabody Society, Class of 2017
American Heart Association Student Scholarship in Cerebrovascular Disease and Stroke****Christopher S. Ogilvy, MD****Department of Neurosurgery, Brain Aneurysm Institute
Beth Israel Deaconess Medical Center**

Aneurysms are persistent, localized dilatations of blood vessel walls. Endovascular therapy for intracranial aneurysms is less invasive compared to surgery and has been associated with favorable outcomes. However, its efficacy remains a central issue due to higher incidence of aneurysm recanalization. With increasing utilization of endovascular techniques in the treatment of both ruptured and unruptured intracranial aneurysms, patients are in need of more comprehensive, streamlined, and accessible risk information. Accordingly, the goal of this study was to develop a stratification scale for predicting all-cause retreatment following endovascular therapy using accessible and widely recognized predictors including aneurysm-specific and treatment-related factors.

We retrospectively reviewed medical records that were prospectively collected for 305 patients who received endovascular treatment for intracranial aneurysms at the Beth Israel Deaconess Medical Center from 2007 to 2013. Multivariable logistic regression was performed on candidate predictors identified by univariable screening analysis to detect independent predictors of retreatment. A composite risk score was constructed based on the proportional contribution of independent predictors in the multivariable model.

Size (>10 mm) ($P<0.0001$; OR=4.90), aneurysm rupture ($P<0.0005$; OR=4.41), stent assistance ($P=0.0481$; OR=0.426), and post-treatment degree of aneurysm occlusion (neck remnant: $P<0.0005$; OR=2.66; residual aneurysm: $P=0.0335$; OR=4.99) were independently associated with retreatment while intraluminal thrombosis ($P=0.135$; OR=9.56) and flow diversion ($P=0.0948$; OR = 0.122) demonstrated a trend towards retreatment. The Aneurysm Recanalization Stratification Scale was constructed by assigning the following weights to statistically and clinically significant predictors: size >10 mm (2 points); rupture (2 points); intraluminal thrombosis (2 points); stent assistance (-1 point); flow diversion (-2 points); neck remnant (1 point); residual aneurysm (2 points). This scale demonstrated good discrimination with a C-statistic of 0.799.

Using this composite risk scale with a range from -2 to +8, we can predict the risk of retreatment as follows: -2, 0%; -1, 4.5%; 0, 9.3%; 1, 14%; 2, 39%; 3, 52.7%; 4, 50%; 5, 90.0%; 6, 100%. No aneurysms in the series were graded 7 or 8.

In conclusion, surgical decision-making and patient-centered informed consent require comprehensive and accessible information on treatment efficacy. We have constructed the Aneurysm Recanalization Stratification Scale to enhance this decision-making process. This is the first comprehensive model that has been developed to quantitatively predict the risk of retreatment following endovascular therapy.

Sleep Disordered Breathing and the Risk of Psoriasis Among US Women**Jeffrey M. Cohen****Harvard Medical School, Walter Bradford Cannon Society, Class of 2015****Abrar A. Qureshi, MD, MPH****Department of Dermatology, Warren Alpert Medical School, Brown University****Joseph F. Merola, MD, MMSc****Department of Dermatology, Brigham and Women's Hospital**

Sleep disordered breathing (snoring and obstructive sleep apnea) is common in the United States and has been associated with negative health outcomes such as diabetes mellitus, cardiovascular disease, and reduced quality of life, presumably due to systemic inflammation. There has been no long-term prospective study on the association between sleep disordered breathing and psoriasis risk.

We prospectively evaluated the association between obstructive sleep apnea and snoring and incident psoriasis and psoriatic arthritis in 71,598 women over an 11 year period (1997-2008) in the Nurses' Health Study. Participants received follow up questionnaires every two years and were asked about snoring, diagnosis of sleep apnea, and diagnosis of psoriasis and psoriatic arthritis. We studied individuals who reported data on snoring and sleep apnea prior to the diagnosis of psoriasis or psoriatic arthritis. The primary outcome was validated physician-diagnosed psoriasis. We used Cox proportional hazards to calculate age-adjusted and multivariate risk ratios.

Over the follow-up period, there were 524 cases of psoriasis among the women who were assessed for sleep apnea. Women with sleep apnea were more likely to have a higher BMI, be hypertensive, work night shifts, and have type 2 diabetes mellitus. The age-adjusted relative risk (RR) of psoriasis among women with sleep apnea was 2.19 (95% CI, 1.39-3.45), the multivariate RR was 1.97 (95% CI, 1.23-3.13). Further adjusting for night shift work, hypertension, cardiovascular disease, and type 2 diabetes mellitus, the multivariate RR was 1.95 (95% CI, 1.22-3.11). There was no effect modification by BMI ($p=0.52$), hypertension ($p=0.34$), or snoring ($p=0.91$). Sleep apnea was not associated with an increased risk of incident psoriatic arthritis. Although women with sleep apnea were more likely to be snorers, we did not find a statistically significant relationship between snoring and the risk of confirmed incident psoriasis.

In this prospective study, we found that obstructive sleep apnea was associated with an approximately two-fold risk of psoriasis among US women. Our results suggest that managing SDB, and in particular OSA, may be a potential target for preventing and managing psoriasis, though our study did not examine this question directly.

High HLA class I antigen expression in combination with low PD-L1 expression as a favourable prognostic biomarker in intrahepatic cholangiocarcinoma**Bradley L. Collins****Harvard Medical School, William Bosworth Castle Society, Class of 2017****Cristina R. Ferrone, MD****Department of General and Gastrointestinal Surgery
Massachusetts General Hospital**

Intrahepatic cholangiocarcinoma (ICC) continues to have an unfortunate prognosis. While little is known about the role of the immune system in ICC, evidence reveals that tumor infiltrating lymphocytes play a major role in the host's immune response to malignancies. This beneficial immune response, however, is suppressed by escape mechanisms utilized by tumor cells. Host cytotoxic T lymphocytes (CTL) can be inhibited by tumor cells expressing PD-L1, which binds to PD-1 on CTLs. Additionally, tumor defects to process and present tumor antigens on HLA class I to CTLs further suppress immune activity. These tumor responses are major impediments to the successful development of immunotherapy treatment.

In this study we evaluate the frequency and distribution of immune infiltrate, the expression of HLA class I antigens, and the expression of PD-1/PD-L1 in 30 ICC tumors. Our aim was to determine whether: ICC patients can develop an immune response against their own tumors, ICC cells express HLA class I antigens, and T-cells/ICC cells express PD-1/PD-L1, respectively.

Thirty patients were randomly selected from ICC patients treated with partial hepatectomy at Massachusetts General Hospital between 2004-2013. Median age was 63 years. The majority of patients had node negative, stage II, and grade 2 tumors. Formalin fixed, paraffin-embedded resection samples were immunohistochemically stained with HLA class I monoclonal antibodies (mAbs), CD8 specific mAbs, and with PD-1/PD-L1-specific mAbs.

All tumors had lymphocytic infiltrate. The number of CD8 T lymphocytes in the fibrous septa between tumor lobules [104.2 (range 9.2-250.0)] was significantly ($P<0.0001$) higher than that within tumor lobules [12.1 (range 0.2-33.7)]. HLA class I antigens were down-regulated in 20 of 30 ICC lesions. PD-L1 was expressed only in 8 out of 30 ICC lesions analyzed. Although no significant correlation was found between overall survival and CD8 infiltrate, HLA class I antigen expression, or PD-1/PD-L1 expression, high HLA class I antigen/low PD-L1 expression was significantly associated with higher patients' survival ($P=0.09$).

Lymphocytic infiltrates were seen in all resected ICC specimens, suggesting a potential patient's immune response to his/her tumor. The potential immune response detected as CD8 infiltrating lymphocytes is affected by the loss of HLA class I antigen expression and the expression of co-inhibitory molecules such as PD-1 and PD-L1. This information provides a rationale for developing immunotherapeutic strategies for ICC patients who may benefit from this type of therapy.

Player Position, Impact Severity, and Brain Chemistry in Retired National Football League Athletes**Jeffrey K. Cooper****Harvard Medical School, Francis Weld Peabody Society, Class of 2017****Alexander Lin, PhD****Center for Clinical Spectroscopy, Department of Radiology
Brigham and Women's Hospital**

Repetitive brain trauma (RBT) from playing American football places athletes at risk for chronic traumatic encephalopathy (CTE), a neurodegenerative disorder characterized by accumulation of hyperphosphorylated tau protein. While all confirmed cases of CTE have had exposure to RBT, not all those exposed develop the disease, suggesting the importance of factors such as impact severity in its development. Skill players and linebackers in collegiate and professional football are known to sustain higher-severity impacts in a typical season than linemen. We thus hypothesized the existence of neurometabolite differences reflective of RBT between these two groups of players.

To test this hypothesis, magnetic resonance spectroscopy (MRS) was used to acquire metabolite concentrations in retired National Football League players (n=45) and age-matched controls (n=15) who were retired non-football professional athletes with no head injury history. Single voxel point-resolved spectroscopy (PRESS; TE=35ms, TR=2s, 2x2x2 cm³) were acquired in four brain regions of interest implicated in earlier single brain injury studies: anterior cingulate gyrus (ACG), posterior cingulate gyrus (PCG), parietal white matter (PWM), and left temporal lobe. This data was then post-processed and partial-volume corrected to measure concentrations of N-acetylaspartate (NAA), glutamate (Glu), creatine (Cr), glutathione (GSH), choline-containing compounds (GPC+PCh), and myo-inositol (mI) using an operator-independent time-domain based fitting of linear combination models (LCModel). Subjects were organized according to head impact severity by NFL position played. Offensive linemen, defensive linemen, and tight ends formed a “moderate risk” group, while running backs, defensive backs, and linebackers made up a “high risk” group. Players were age-matched and unpaired t-tests were used to assess group differences.

The moderate-risk group showed a higher concentration of Glu when compared with controls; however, the high-risk group exhibited a significantly lower Glu concentration (p=0.008) and Cr concentration (p=0.04) within the PCG than the moderate-risk group. These data support a RBT model in which Glu and Cr initially show an excitotoxic increase in the PCG followed by a sharp decline with increasing impact severity, possibly reflecting neuronal degeneration. While CTE is a disease that manifests with brain-wide pathological changes, our findings were restricted to the PCG. It thus cannot be excluded that these results may reflect a pathology of focal neural atrophy distinct from CTE. Future studies should assess the role of head trauma severity in pathological changes of RBT, and an ongoing assessment of RBT epidemiology in football players is needed, as rule changes and protective equipment may change impact severities reported here.

Understanding variation in macrophage cell death following *M. tuberculosis* infection: A systems biology approach

Robert M. Crutcher

Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Bree Aldridge, PhD

**Department of Molecular Biology and Microbiology
Tufts University School of Medicine**

Mycobacterium tuberculosis (Mtb) infects a third of the world's population and is responsible for 2 million deaths each year. The virulence of Mtb, an intracellular pathogen that replicates in the alveolar macrophage, depends on complex interactions with the host immune system. In the last decade, macrophage cell death phenotypes have been recognized as important determinants of the outcome of Mtb infection. Macrophage apoptosis is considered beneficial to the host because it inhibits bacterial replication and sequesters bacteria in membrane-bound compartments. Virulent strains of mycobacteria subvert macrophage apoptosis and cause necrosis, a lytic form of cell death that enables the spread of the bacterium to other host cells.

To quantitatively navigate the complexity of the Mtb-macrophage interaction, we have developed a mathematical model to simulate the race between the signal transduction pathways upstream of apoptosis and necrosis. These pathways are initiated by pathogen associated molecular patterns (PAMPs) recognized by Toll-like receptors (TLRs) and inflammasomes, and modulated by cytokines such as TNF. Our model topology builds on published mass action kinetics models for NF- κ B, mitogen-activated protein kinase (MAPK), and caspase signaling, and includes several key features of macrophage cell death highlighted in the recent literature such as eicosanoid synthesis, mitochondrial depolarization, oxidative stress, and membrane degradation.

In the coming months we will use our model to explore hypotheses about how virulent strains of mycobacteria alter the necrosis-apoptosis balance. Several potential virulence mechanisms have been put forth in the recent literature, including cyclooxygenase inhibition and membrane pore formation. Using Luminex XMAP technology, we will quantitatively measure protein levels in macrophages infected with Mtb and the virulence-attenuated *M. bovis*-derived Bacille Calmette-Guérin (BCG) vaccine strain. Using Markov Chain Monte Carlo (MCMC) Bayesian analysis, we will incorporate the data from these time course experiments into our model parameters. We will use this information to deduce where potential virulence factors may act on host cell signaling pathways. Knowledge of these virulence mechanisms will be crucial to the design of targeted therapies and more effective vaccines for tuberculosis.

Caries Associated Bacteria and Cariogenic Diets as Risk Factors for Early Childhood Caries

Veronica A. De Armas

Harvard School of Dental Medicine, Oliver Wendell Holmes Society, Class of 2017

Anne C.R. Tanner, BDS, PhD

The Forsyth Institute, Department of Microbiology

Streptococcus mutans and *Streptococcus sobrinus* are the principal species that have been studied in dental caries. A novel species, *Scardovia wiggsiae*, was found to be associated with severe early childhood caries (ECC). ECC is a problem worldwide and it affects 28% of US children. By studying *S. mutans*, *S. sobrinus*, and *S. wiggsiae* in addition to other risk factors for ECC, we hypothesize that we can improve risk assessment for ECC.

Children with and without ECC were recruited from a community dental center. A survey completed by the child's caregiver included the child's demographics, dental and dietary habits. Child caries, plaque and gingivitis were recorded. Saliva was collected and DNA purified. *S. mutans*, *S. sobrinus*, and *S. wiggsiae* were measured using quantitative-PCR for bacterial presence and levels. Bacterial DNA levels were converted to bacterial cell counts (levels). Survey and bacterial data were compared between ECC and caries-free and/or low caries children using non-parametric tests (Mann Whitney U, and Chi square tests).

One hundred and fifty children were studied. Data was compared between 76 children with no-to-very-low caries and 74 children with ECC. Clinical groups did not differ in age (mean 5.2 years), number of teeth (mean 19 deciduous teeth) or plaque, gingivitis and bleeding on probing scores. More children with ECC were covered by Maine Care insurance ($p=0.018$), and had a greater consumption of chips ($p=0.008$) and popcorn ($p=0.07$) than low/caries-free children. More low/no caries children consumed dried fruit ($p=0.012$) than ECC children. *S. mutans* detection frequency ($p = 0.05$) and levels ($p=0.01$) were higher in ECC than for low/no caries children. While *S. wiggsiae* detection frequency did not differ between groups (39 % ECC versus 36% low/caries-free), the mean levels were higher in the ECC children ($p= 0.291$) but not significantly. Data for *S. sobrinus* is under analysis for conversion to colony counts.

In conclusion, ECC in this population was associated with low SES (measured by health insurance) and a cariogenic diet, particularly chips. The association of *S. mutans* with ECC was confirmed. Although not statistically significant, an association with *S. wiggsiae* and ECC was observed. It is likely that adding *S. wiggsiae* from saliva will improve risk assessment for ECC.

An Exploration of the Life and Work Landscape of Domestic Workers**Daniela Delgado****Harvard Medical School, Walter Bradford Cannon Society, Class of 2017****Dr. Barbara Gottlieb****Harvard Medical School****Harvard School of Public Health**

Domestic workers are simultaneously some of the most critical caregivers and among the most marginalized workers in the United States. This workforce, including housekeepers, nannies, and home health aides, is comprised primarily of immigrant women and women of color. According to the American Community Survey (ACS), in 2010 there were 726,437 domestic workers in the U.S. Others have estimated about 2.5 million women working as domestic workers. With a lack of legal protections this already vulnerable population is subject to abuse, low pay and mistreatment. According to a recent study by the National Domestic Workers Alliance (NDWA), 67% of those who live with families are paid below the state's minimum wage. Domestic work can also be hazardous, with exposure to toxic chemicals and long work days. There are few studies of these workers' health and well-being, and no studies that simultaneously query employers' perceptions. This study aims to characterize the health needs and potential threats to the well-being of domestic workers in the Boston area according to the workers and their employers.

A community-based participatory action research (CBPAR) approach is used in this project. In collaboration with MataHari, the community partner organization, two focus groups with domestic workers (n=17), two in-depth interviews with workers and three with employers were conducted. Using directed content analysis, a qualitative analytic strategy, the following 4 main themes emerged from the combined qualitative data: 1.) Physical and mental health and well-being (e.g. workplace safety), 2.) Unfair treatment and vulnerability (e.g. housing instability), 3.) Basic worker rights and advocacy (e.g. paid sick days) and 4.) Can employers be allies? Consistent with the CBPAR model, a member check-in was conducted, where the themes generated were presented to a group of workers making sure these are valid and meaningful to them.

This study highlights the health risks for domestic workers and illustrates avenues for programmatic initiatives. For example, the partner organization is developing educational sessions for employers, potentially mitigating the unfair treatment of this profession. Furthermore, Massachusetts recently passed the Domestic Workers Bill of Rights. This investigation can serve as a foundation for future research to explore the relationship between lack of fundamental workers' rights and adverse health. In addition, this can support advocacy efforts on behalf of these vulnerable workers.

The Impact of Oral Chronic GVHD on Global Measures of Quality of Life**Joseph R. DePalo****Harvard School of Dental Medicine, Francis Weld Peabody Society, Class of 2017****Nathaniel S. Treister, DMD, DMSc
Department of Oral Medicine and Dentistry
Brigham and Women's Hospital****Corey S. Cutler, MD, MPH
Medical Oncology
Dana-Farber Cancer Institute**

Chronic graft-versus-host disease (cGVHD) is a frequent complication of allogeneic hematopoietic stem cell transplantation (HSCT) and a leading cause of long-term morbidity and non-relapse mortality. Approximately 30-70% of HSCT recipients develop some degree of cGVHD, which can manifest in a number of anatomic locations. The oral cavity is one of the most frequently affected sites, with manifestations characterized by lichenoid mucosal inflammation with associated pain and sensitivity, as well as salivary gland hypofunction with associated xerostomia and dry mouth-related complications. Long-standing oral cGVHD can be associated with daily pain and suffering, compromised nutritional intake, rampant dental decay and tooth loss, and an increased risk of oral squamous cell carcinoma.

Chronic GVHD is a major cause of reduced quality of life (QOL) post-HSCT. It has been shown that patients with cGVHD are more likely to report decreased global measures of QOL compared to those without a history of cGVHD. Despite this understanding, the impact of organ-specific involvement on global QOL measures is poorly understood. Studies analyzing the association between oral involvement and global QOL measures are limited and have produced varying results.

To address this gap in our understanding, this study sought to assess the contributions of oral cGVHD to global measures of QOL. Data on QOL was obtained for 569 patients from the Chronic GVHD Consortium, a multi-center observational cohort of allogeneic HSCT recipients that were ≥ 2 years of age and affected by cGVHD requiring systemic immunotherapy. Subjects were grouped according to cGVHD oral involvement (isolated oral involvement, oral and concomitant extra-oral involvement, and extra-oral involvement only) and compared on the basis of QOL scores obtained using FACT-BMT and SF-36 QOL instruments.

On average, subjects with isolated oral involvement reported better QOL when compared to subjects with oral and concomitant extra-oral involvement. However, the data also indicate that oral cGVHD involvement adversely impacts multiple QOL domains. Furthermore, the results suggest that the FACT-BMT instrument may be better suited for assessing QOL in oral cGVHD patients, given that FACT-BMT measured QOL scores were more sensitive in comparison to equivalent scores provided by the SF-36 instrument.

This study was limited by sample size, particularly in terms of patients with isolated oral involvement (n=22). The analysis was also limited by the definition of oral involvement, which greatly simplified a complex disease with highly variable clinical characteristics.

Platelet depletion in mice with VT accelerates thrombus resolution and decreases thrombus neovascularization

Elise DeRoo

Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Denisa Wagner, PhD

**Program in Cellular and Molecular Medicine
Boston Children's Hospital**

Venous thromboembolism (VTE), which encompasses both venous thrombosis (VT) and pulmonary embolism (PE), is a major health problem. Each year approximately 1 million people are affected by VTE in the US alone. Understanding the mechanisms that underlie venous thrombosis is crucial to developing safe and effective therapies.

It is known that platelets play a significant role in thrombogenesis. Although the role of platelets in thrombus initiation is well understood, their importance during the later stages of VT remains unclear. We investigated the influence that platelets have on thrombus composition, maturation, and resolution during the later stages of VT. Specifically, we investigated how platelet depletion in mice with VT impacts thrombus volume and neovascularization, a phenomenon commonly observed in maturing thrombi that is not yet well understood in the context of VT.

We hypothesized that platelet depletion would accelerate thrombus resolution and decrease thrombus neovascularization. To test these hypotheses, starting 18 hours after surgically inducing thrombosis in the inferior vena cava (IVC) of C57BL/6 mice, we depleted platelets (>90% depletion) using a monoclonal anti-platelet antibody. We followed the mice for changes in thrombus volume over time using ultrasound and harvested IVC/thrombus tissue samples 8 days post-surgery for histological analysis. Control mice received a non-platelet depleting control antibody.

Thrombi harvested from platelet-depleted mice on post-surgical day 8 were shorter in length ($p < 0.01^*$) than thrombi harvested from control mice. Depleting platelets had no effect on the change in thrombus volume between days 1 and 4 ($p = 0.5918$), but tended to accelerate thrombus resolution between days 4 and 8. This difference in resolution rate approached statistical significance ($p = 0.18$). The histological features observed in thrombi from platelet-depleted mice were strikingly different from those observed in 8-day-old thrombi harvested from control mice. Thrombi from control mice were rich in cells that appeared to be forming vascular structures branching off the IVC endothelium and stained positive for PECAM (endothelial cell marker). Thrombi from platelet-depleted mice showed reduced PECAM staining and less neovascularization as compared to controls.

These data suggest that platelets play an important role not only in the very early stages of thrombogenesis, but also in thrombus maturation, resolution, and neovascularization. In the future, we will examine several other markers of neovascularization in our tissue samples, and we will seek to better understand the role that thrombus neovascularization plays in thrombus maturation and resolution.

Non-Additive Effects of HLA Genes in Three Common Autoimmune Diseases**Aaron J. Deutsch****Harvard Medical School, Irving M. London Society, Class of 2017****Soumya Raychaudhuri, MD, PhD****Divisions of Genetics and Rheumatology, Department of Medicine
Brigham and Women's Hospital**

Autoimmune diseases represent a spectrum of conditions that affect up to 5% of the human population. A common feature of these diseases is that the human leukocyte antigen (HLA) genes within the major histocompatibility complex (MHC) influence susceptibility by altering the binding repertoire of antigenic peptides presented to T cells.

Most studies of complex human diseases assume an underlying architecture of additive genetic variants, in which effect sizes combine in a linear fashion. However, non-additive effects can occur when genes interact with one another, either at the same locus (dominance) or across separate loci (epistasis). We investigated whether non-additive effects within the HLA genes play a role in disease susceptibility. Because individuals who are heterozygous at a specific HLA gene possess an expanded binding repertoire, we speculated that a non-linear model might yield better predictions of disease susceptibility.

In this study, we examined genome-wide SNP genotype data from three common autoimmune diseases: rheumatoid arthritis (RA), type 1 diabetes (T1D), and psoriasis vulgaris (PsV). In each case, we applied a powerful and accurate HLA imputation algorithm devised by our group to infer classical HLA allele genotypes. We focused on the HLA gene with the strongest association to each disease (RA: *HLA-DRB1*; T1D: *HLA-DQB1*; PsV: *HLA-C*). We constructed logistic regression models to compare the genetic contribution to disease risk in three scenarios: additive effects only, additive plus dominance effects, or additive plus within-locus interaction effects.

For all three diseases, we found that the inclusion of non-additive terms significantly improved the fit of the model (RA: $P = 1.3 \times 10^{-10}$; T1D: $P = 7.0 \times 10^{-26}$; PsV: $P = 4.0 \times 10^{-8}$). The improved models explained an additional 0.9%, 2.2%, and 0.2% of phenotypic variance for RA, T1D, and PsV respectively. One explanation for this observation is that within locus HLA interactions produce non-additive effects. Indeed, the inclusion of within-locus interaction terms significantly improved the model for RA ($P = 3.5 \times 10^{-3}$) and T1D ($P = 3.2 \times 10^{-48}$), but not for PsV ($P = 0.87$).

Overall, our results provide exciting first insights into a previously underestimated aspect of the genetic architecture of autoimmune diseases: non-additive effects of allelic variants at co-expressed loci. RA and T1D (primarily associated with MHC class II genes) showed evidence of within-locus interactions, while PsV (primarily associated with an MHC class I gene) did not. This suggests that the nature of non-additive effects may differ between MHC class I and class II genes.

**Comparative Patient-Reported Quality of Life Outcomes in the NC ProCESS
Cohort Following Treatment of Prostate Cancer by Robotic Prostatectomy,
Intensity-Modulated Radiation, and Stereotactic Radiation**

Kevin Diao

Harvard Medical School, William Bosworth Castle Society, Class of 2017

Ronald C. Chen, MD, MPH

**Radiation Oncology Department, Lineberger Comprehensive Cancer Center
The University of North Carolina at Chapel Hill**

Every year in the United States, 240,000 men are diagnosed with prostate cancer. Approximately 90% of prostate cancers are potentially curable, but treatments can cause side effects that decrease the quality of life for prostate cancer survivors. Side effects range widely in severity and time course and can significantly alter patients' quality of life thereafter. New treatment techniques such as intensity-modulated radiation therapy that use more complex, varying intensity radiation beams have a theoretical advantage of being able to decrease incidental radiation dose to the bladder and rectum. However, there is relatively little published data on the quality of life outcomes of modern prostate cancer treatments, including robotic prostatectomy, intensity-modulated radiation, and stereotactic radiation. The research project provides data on quality of life outcomes in patients treated with these modern techniques in the community.

The North Carolina Prostate cancer Comparative Effectiveness and Survivorship Study (NC ProCESS) is a large, population-based cohort of 1,500 prostate cancer patients who were enrolled at diagnosis from across North Carolina, and are being followed longitudinally for their treatment outcomes and self-reported quality of life. As part of the process, patients were contacted at regular time intervals to complete a comprehensive quality of life questionnaire. Furthermore, clinics and hospitals that the patients were seen at for medical care were contacted to retrieve all relevant medical records. Comorbidities were extracted from the medical records. Comorbidities were summarized and it was found that the most common comorbid conditions were hypertension (60%), hypercholesterolemia (55%), back pain (47%), arthritis (39%), and diabetes (23%). Furthermore, demographic information regarding the patient cohort was collected and summarized. The median age of participants was 65 and 66% of the cohort had at least some college education. The most common household income bracket of participants was \$40,000-\$70,001 while 45% of participants listed "retired" as their employment status.

Quality of life data continues to be collected on a rolling basis from the study participants; when 3 month and 12 month patient questionnaire and medical record data is completed for the cohort, we will begin comparative analysis of patient outcomes.

Characterization and outcomes of severe primary multi-vessel pulmonary vein stenosis in low-birth weight infants

Ashley Dickens

Harvard Medical School, Francis Weld Peabody Society, Class of 2017

Christopher Baird MD

Department of Cardiac Surgery

Boston Children's Hospital & Harvard Medical School

Primary pulmonary vein stenosis (PVS) is generally the most aggressive form of the disease; infants are often born premature and develop signs and symptoms within weeks to months after birth and frequently do not survive. The aim of this study was to characterize primary PVS in young pre-mature infants and evaluate outcomes following surgical intervention.

Patients undergoing surgical repair for PPVS from February 2008 to July 2014 at Boston Children's Hospital were identified. Demographic information, pulmonary vein (PV) characteristics, interventional findings, and available follow-up data were retrospectively collected from the medical record. Survival was determined by Kaplan-Meier analysis.

Twenty-five patients were identified with severe multi-vessel primary PVS. Median gestational age at birth was 34 weeks (25-40) and weight was 1.54 kg (0.39-4.22). Most patients underwent a pre-operative CT scan. The common findings included the following: right upper PV associated with the right pulmonary artery, left upper PV associated with the left bronchus and left lower PV associated with the descending aorta and left lung atelectasis. The right lower PV was generally unaffected. At operation, median age was 5.8 months (1-35) and weight was 4.9 kg (2.7-14). 92% had bilateral PV disease and 84% had involvement of three or more PV. The most common PV involved was RU (96%), LU (88%) and LL (80%) while the RL PV was involved least (44%). PV atresia was found in nearly half the patients (48%) and most commonly associated with the RU PV (28%) and LU PV (16%). All patients underwent post-operative catheterizations and 22 patients (88%) had interventions. The median number of catheterizations per patient was 3 (1-13). The median number of catheterizations with intervention per patient was 2.5 (1-12). No patients had PV re-operation. One patient died within 30 days following operation and 11 patients (44%) died in the follow-up period at a median follow-up of 0.8 years (13 days-5.2 years). Eight patients were listed for lung transplantation: three patients were de-listed, three patients died waiting and two patients were transplanted.

Severe multi-vessel primary PVS is uniformly fatal if not intervened upon. The role of extrinsic anatomic structures may need to be looked at when considering treatment. Aggressive multi-modal medical, surgical and interventional approach has improved survival in these patients, but mortality remains high. Continued characterization of primary PVS in neonates and infants will help to identify these patients earlier to prevent progression and allow earlier intervention and continued improved survival.

Assessing Palliative Care Needs of Oncology Patients in Mirebalais, Haiti**Sarah-Bianca G. Dolisca****Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017****Lawrence N. Shulman, MD****Department of Medical Oncology****Dana Farber Cancer Institute and Brigham and Women's Hospital**

Introduction: Partners in Health/Zanmi Lasante is the only provider of free cancer services in Haiti. The adult oncology program was launched three years ago by an interdisciplinary team, which has worked to formalize and integrate services for patients with cancer and build skills through training. There is limited data on the use of palliative care including pain management and psychosocial support within the clinic. Data collection on patient palliative care needs will be used to support the improvement of cancer care delivery at University Hospital in Mirebalais.

Methods: To determine the scope of palliative care needs and services in order to set future implementation priorities, we interviewed a consecutive sample of 40 patients presenting for treatment, routine outpatient cancer care, or treatment specific support groups at the University Hospital in Mirebalais in July 2014. We developed and implemented a structured interview through use of the African Palliative Outcomes Scale to assess demographic, physical, psychological, social and spiritual concerns that includes both the needs of the patient and their family. The answers to questions were scored using a Likert scale from 0 to 5.

Results: 40 patients interviewed were diverse in age (mean +/- SD) 45 +/- 11 and predominately female (88%). 70% of the study population identified as unemployed. Over three-quarters of patients (n=31) had breast cancer as their primary diagnosis. The highest cited need of the study population included the desire for good health, help securing a job or financial income, and having a doctor or nurse visit the patient in the home. A moderate amount of patients indicated elevated degree of pain and worry associated with their disease course.

Preliminary Conclusions: The data reveals a moderate level of pain and unmet psychosocial needs among patients with cancer in Mirebalais, Haiti. Increased emphasis on development of social supports including home based care and connecting patients with disability resources and employment opportunities may be services that PIH / ZL can facilitate to improve care for patients.

Limitations: The study is comprised of a relatively small convenience sample of patients which weakens the external validity of the study. This study will serve as a pilot to inform the development of a larger study

Defining the Mechanism Underlying Micronuclei-Mediated Mutagenesis in Cancer**Bridget M.J. Donovan****Harvard Medical School, Walter Bradford Cannon Society, Class of 2017
Miliotis Fellowship in Pediatric Oncology****David Pellman, MD****Department of Cell Biology, Pediatric Oncology
Dana-Farber Cancer Institute**

Cancer cells exhibit high degree of genome instability including numerical and structural chromosome aberrations, as well as abnormal nuclear structures, such as micronuclei and chromosome bridges. Micronuclei are small extranuclear organelles containing whole chromosomes or chromosomal fragments that arise through aberrant cell division, replication errors or exposure to exogenous genotoxic agents.

Previous work from the Pellman laboratory suggested that whole chromosome missegregation into a micronucleus in mitosis leads to acquisition of massive DNA damage following entry into S-phase in a replication-dependent manner. Unrepaired damage can be inherited by cell progeny through micronucleus reincorporation in subsequent mitoses. DNA damage in micronuclei is also associated with a rapid, irreversible disruption of the nuclear envelope (NE) integrity in interphase, and occurs primarily when NE rupture is coincident with ongoing replication. Since micronuclei exhibit DNA replication and abnormal localization of key replication factors including Replication Factor A (RPA) and subunits of DNA helicase, we hypothesized that replicating micronuclei may be subject to increased replication stress leading to long stretches of single-stranded DNA (ssDNA), thus providing a substrate for cytoplasmic nucleases upon rupture.

In order to test the hypothesis, we assessed the extent of single-stranded DNA (ssDNA) present in micronuclei in S phase using a native BrdU assay. We observed fewer BrdU foci in intact replicating micronuclei as compared to primary nuclei, pointing to less efficient replication. Even upon induction of replication stress in the setting of ATR inhibition that leads to massive dormant origin activation in primary nuclei and subsequent replication catastrophe, we observed minimal increase in BrdU foci in intact micronuclei, suggesting that micronuclei may have few functional origins of replication. In contrast, micronuclei with disrupted NE exhibited dense clusters of BrdU foci. Since these micronuclei are not expected to undergo further replication upon loss of membrane integrity, we postulate that the observed foci likely represent the sites of DNA double-strand breaks that form upon NE rupture in the setting of DNA replication.

These results point to a defect in origin licensing as a cause of replication delay in micronuclei, thus providing a link between aberrant replication and mutagenesis. Understanding the process by which micronuclei lead to accumulation of DNA mutations and tumor formation will accelerate the development of effective therapeutic strategies for patients whose cancers arise as a consequence of micronuclei-mediated mutagenic events.

**Preoperative Malalignment and Total Knee Replacement Outcomes
In a Developing Nation**

Daniel A. Driscoll

Harvard Medical School, Francis Weld Peabody Society, Class of 2017

Jeffrey N. Katz, MD, MSc

**Director, Orthopaedic and Arthritis Center for Outcomes Research
Brigham and Women's Hospital**

Total joint replacement (TJR) is used to treat advanced osteoarthritis and has been shown to be effective in increasing function and reducing pain levels in individuals for whom more conservative osteoarthritis treatment has proven ineffective. TJR is performed routinely in the developed world but availability of TJR in the developing world is limited. Operation Walk Boston is an annual orthopedic mission trip that provides knee and hip replacements to persons with advanced arthritis in the Dominican Republic, a developing country, who would otherwise be unable to receive a replacement.

We hypothesized that patients with preoperative knee malalignment would have (1) more pain and less function before total knee replacement (TKR) and (2) similar net improvement in pain and function after TKR compared to patients with neutrally-aligned knees. In order to test these hypotheses, patients with osteoarthritis who received TKR from 2008 to 2013 from Operation Walk were studied (n=137). Patients were given Western Ontario and McMaster University Osteoarthritis Index (WOMAC) and Short-Form 36 surveys before TKR and one or two years after TKR in order to measure pain and function. Preoperative anatomic tibiofemoral angle was measured using short, standing AP radiographs and served as measures of knee alignment.

Before TKR, seventy-eight patients (56.9%) had varus knee malalignment, twenty-eight (20.4%) had valgus knee malalignment, and thirty-one (22.7%) had neutral knee alignment. The three groups showed minimal variation in WOMAC Function and SF-36 scores, both before and after surgery. The varus patient group demonstrated the smallest mean preoperative WOMAC pain score (61.5) compared to the valgus (66.0) and neutral (68.6) groups. The valgus patient group had a lower mean follow-up WOMAC pain score (10.2) compared to the varus (18.1) and neutral groups (15.5). The valgus group showed a mean WOMAC pain score improvement of 55.9 compared to 49.0 in the neutral group and 44.1 in the varus group.

These data suggest that patients with varus knee malalignment have the least pain before TKR while patients with valgus knee malalignment have the (1) least pain and (2) greatest reduction in pain after TKR. These results may help physicians to better understand total knee replacement outcomes and to more effectively communicate with patients regarding therapeutic expectations of TKR.

Mandatory geriatric consult on elderly trauma patients: an evaluation of patient outcomes and costs**Maria J. Duarte****Harvard Medical School, William Bosworth Castle Society, Class of 2017****Zara Cooper, MD****Department of Surgery****Brigham and Women's Hospital**

Introduction: Major demographic shifts have caused epidemic of injured elders in recent years, mostly due to falls. Advanced age is a risk factor for poor outcomes after traumatic injury, independent of severity of injury, co-morbidities, or region of injury. Older patients experience higher rates of mortality and complications, longer hospital stays, and, and are more likely to be discharged to institutions than their younger counterparts.. Moreover, they are often frail, have multiple medical comorbidities, and complex social needs making them a particularly challenging group to treat. In order to better meet the needs of older trauma patients and their families, The Brigham and Women's Hospital Division of Trauma, Burns and Surgical Critical Care introduced a board certified geriatrician to the multi-disciplinary team caring for older trauma patients at its Level I trauma center. A geriatrician consults on all patients > 70 years within 72 hours of admission to the trauma service, providing a complete geriatric assessment, recommendations for management of medical issues and longitudinal follow up throughout the hospital stay. The purpose of this study is to evaluate the impact of routine geriatric consultation on outcomes during hospitalization, as compared to historical controls.

Methods: We will include patients >70 years admitted to the BWH trauma service and seen between October 1, 2013 and September 30, 2014. and historical controls > 70 years admitted between October 1, 2011, and September 30, 2012. Data will be collected from the BWH trauma registry and chart review and will include patient demographics, injury diagnosis and severity, cognitive and functional status, comorbidities, hospital length of stay, complications, procedures, and discharge disposition. The primary outcome is hospital length of stay. Secondary outcomes include delirium, unplanned ICU admission, change in code status, and medication management (i.e. narcotics, benzodiazepines, and antipsychotics). We will report frequencies, means, standard deviations and interquartile ranges where appropriate. We will use Chi Square and Wilcoxon Rank Sum to measure differences between groups. We will use multivariate analysis to identify independent factors associated with length of stay, admission before or during the intervention. .

Results: It is estimated that 220 patients in the intervention arm will be compared to 211 historical controls. Analysis will be complete pending final data collection

Conclusions: These results will help elucidate the effect of routine geriatric consult for injured elders. Improved outcomes could set a new standard for care of the older patients in level 1 trauma centers.

**Validating an Oral Health Indicator Survey Tool to Accurately and Efficiently Capture
Malnutrition and Oral Health Data**

Yianni Ellenikiotis

Harvard School of Dental Medicine, Oliver Wendell Holmes Society, Class of 2017

Karen Sokal-Gutierrez, MD, MPH

Community Health and Human Development

UC Berkeley-UCSF Joint Medical Program

Brittany Seymour, DDS, MPH

Global and Community Health

Harvard School of Dental Medicine

Children in developing nations are vastly affected by malnutrition and tooth decay with rates of tooth decay increasing over the last several years. Oral health diseases have been recognized as significant problems affecting approximately 2.1 billion individuals worldwide, yet little attention has been given to improving oral health.

Oral diseases negatively impact child nutrition, child growth, child well-being, and general life satisfaction. In the Amazonian regions of Ecuador, up to 88% of young children have untreated tooth decay, 30-40% have malnutrition, and 43% have mouth pain. We aimed to work with several different Amazonian and mountainous communities in Ecuador in attempts to evaluate the effectiveness of interventions focused on reducing child malnutrition and oral health diseases by educating communities on oral health and nutrition, distributing toothbrushes and toothpaste, and providing fluoride varnish. Additionally, we planned to validate an oral health indicator survey tool that could lead to more efficient oral health data collection that can become part of existing demographic health surveys. With increased data collection, we are hopeful that global policies could be better tailored for oral disease interventions.

We worked with seventeen different indigenous tribes in the amazon jungle and saw over 700 children aged 6 months to 6 years in the Amazonian region called Pueblo Kichwa. We also partnered with the Ecuadorian dental and public health school of Universidad San Francisco de Quito and reached out to approximately 200 children aged 6 months to 15 years in mountainous communities. As part of the intervention, we additionally surveyed parents and screened for malnutrition and severe childhood caries. We referred those children that had tooth decay to dentists at the Ministry of Health to ensure appropriate treatment. Our primary analysis will focus on examining the relationships between self-reported oral health outcomes and actual prevalence of severe early childhood caries and/or malnutrition to determine predictive value. We will perform a simple regression and correlation analysis using prevalence of severe early childhood caries as our dependent variable and evaluating multiple self-reported health outcomes as independent variables.

The generalizability of this project could be in question because we worked with specific populations in Ecuador, however we believe malnutrition and tooth decay continue to be a problem for children all over developing nations and developed nations alike. As access to and consumption of unhealthy and sugary foods become increasingly common in developing nations, tooth decay and malnutrition rates will continue to rise and negatively impact child health rise unless successful interventions are developed to combat this.

Exploring the Use of Financial Incentives in a Smoking Cessation Program for Homeless People: Assessing Correlates of the Amount of Money It Will Take to Quit

Sally Engelhart

Harvard Medical School, Francis Weld Peabody Society, Class of 2017

Travis Baggett, MD MPH

**Division of General Internal Medicine, Massachusetts General Hospital, Boston
Health Care for the Homeless Program**

Smoking is a major cause of morbidity and mortality among homeless individuals, with over 70% of the homeless adult population smoking. To improve the health and reduce the health care costs of this population, it is critical to provide effective smoking cessation programs. Financial incentives are a promising way to interest homeless persons in cessation programs and to improve success rates. The aim of this exploratory study is to gauge the dollar value that homeless smokers put on smoking, and to determine what factors correlate with this dollar value. Through this study, we hope to identify which individuals may be more or less responsive to the use of financial incentives in cessation programs.

We recruited 309 homeless smokers from 5 Boston Health Care for the Homeless Program clinics to complete a 30-45 minute survey. I administered many of these surveys as a field interviewer on the research team. The question gauging the dollar value put on smoking was: *Suppose someone would pay you money to quit smoking. How much money would it take to quit smoking for...[open-ended response format] 1 day? 1 week? 1 month? 1 year?* Other questions covered demographics, smoking behavior, beliefs related to smoking, health issues, subsistence issues, substance use and psychiatric illnesses.

The median responses and interquartile ranges for the amount of money needed to quit for 1 day, 1 week, 1 month and 1 year were \$50 [\$20-100], \$200 [\$70-700], \$600 [\$200-2000] and \$3000 [\$1000-10,000], respectively, and the number of responses to each question were 280, 276, 270 and 261. In the coming months, we will conduct analyses to identify which factors correlate with these median responses.

As expected, the median responses increased for longer time frames. The distribution of responses was broad and non-normal, with a small number very high outliers. My observation as an interviewer was that individuals who responded with very high dollar amounts were not seriously considering the hypothetical question.

The number of responses declined as the questions progressed to longer time frames, possibly reflecting increasing conceptual difficulty in attaching a dollar value to the distant future. The major limitation of this study is that the survey items gauging the dollar value put on smoking were pretested but not rigorously, psychometrically validated. Consequently, some participants may not have understood the items, and the items may not accurately reflect the true amount of money it would take to motivate quitting.

Identifying and Addressing Barriers to Self-Management Care for Patients with Diabetes**Imarhia Enogieru****Harvard Medical School, Walter Bradford Cannon Society, Class of 2017****Scot Sternberg, MS, Nisha Basu, MD, MPH****Center of Primary Care Innovations Fellows Program, Healthcare Associates,
Beth Israel Deaconess Medical Center**

There are 25.8 million Americans with diabetes. In patients with diabetes, a $HbA1c \geq 8$ is associated with increased risks of myocardial infarction, stroke, nephropathy and retinopathy. Reductions in $HbA1c$ have been achieved by promotion of self-management, use of multidisciplinary teams and expansion of nursing roles.

As Healthcare Associates (HCA) at Beth Israel Deaconess Medical Center (BIDMC) transforms into a patient centered medical home, Team 4 is incorporating population management, team-based care, and quality improvement strategies to reduce the number of patients with $HbA1c \geq 8$. Objectives of this study include identifying barriers to self-management for patients with $HbA1c \geq 8$ and engaging the team LPN to facilitate patients' access to internal and external resources that can address patients' barriers.

The intervention begins with medical assistants identifying patients with $HbA1c \geq 8$ during their huddle with primary providers. Once patients arrive for their visit, the medical assistants give patients the "DM Intake Sheet" packet. It includes an assessment comprised of a subset of questions from the validated Self-Management Profile for Type 2 Diabetes (SMP-T2D) questionnaire, a Diabetes Care Profile (DCP) and the Patient Health Questionnaire (PHQ-2). This 2-page assessment screens patients for depression (PHQ-2) and asks patients to identify any difficulties with access to healthy foods, medication adherence, blood glucose monitoring, and exercising.

Patients complete the assessment and providers review it. If a barrier is identified, providers use the third page of the packet to communicate with the team LPN about patient follow up. The LPN meets with the patient face-to-face and/or by phone. She (1) reviews patients' care plan, (2) uses motivational interviewing to help patients establish goals for self-management, and (3) connects patients to resources that can help them address their barriers. In the initial two months of this intervention, fifteen patients received the assessment; fourteen indicated a barrier to self-management. The most common barriers are difficulty managing weight (57%) and difficulty managing exercise (50%). Eight of those patients had LPN follow up; the other six patients get care with Joslin Diabetes Center. Five of the LPN follow up patients were referred to other internal and external resources. Process and data collection is on-going. Future measures will include changes in $HbA1c$.

Patients' barriers to self-management are being identified and addressed through LPN follow up or other healthcare professionals. Review of the assessment during the patient visit can be challenging. Integrating the team LPN in the review process is an effective alternative.

**Limited-English Proficient Ischemic Stroke Patients' Care and Clinical Outcomes:
Findings from the Get With The Guidelines–Stroke Program**

Betty Man-Ling Luan Erfe
Harvard Medical School, Walter Bradford Cannon Society, Class of 2017

Nicte I. Mejia Gonzalez, MD
Department of Neurology
Massachusetts General Hospital

Stroke is the fourth leading cause of death and disability in the United States with associated high human and economic costs. In the U.S., 750,000 new strokes occur every year, leaving half of its survivors with physical and cognitive disabilities that make performing daily activities difficult. Strokes accounted for about \$73.3 billion of total health expenditures in 2010. By increasing the quality and consistency of care for all stroke patients, we can improve health outcomes and reduce overall health expenditures.

According to the 2011 Census, 17.2% of survey respondents or 60,577,020 individuals speak another language other than English at home. In the Boston-Cambridge-Quincy area of Massachusetts, there are a total of at least 393,000 limited-English proficient (LEP) individuals, among whom 37,200 speak Spanish and the remaining speaking Portuguese, Chinese, Haitian Creole, Vietnamese, Khmer, Cape Verdean, Russian, Arabic and Korean.

With the population seeking medical care becoming increasingly linguistically diverse, we can improve health outcomes and reduce overall health expenditures by raising the quality and consistency of care for all stroke patients. No study to date examines how limited-English proficiency impacts care and outcomes for stroke patients. We assessed the hypothesis that a patients' LEP status is associated with poorer performance in pre-hospital management and in-hospital treatment measures, and worse in-hospital outcomes.

We analyzed data from 3,894 patients (307 LEP, 2989 English-proficient patients) discharged from MGH between 1/1/2003 and 4/30/2014 with acute ischemic stroke as the primary admission reason and with a known language preference.

Compared with English-proficient patients, LEP patients were more likely to have Medicaid or be uninsured (2.9%v0.8%, 6.2%v1.7%, $p<0.0001$), to live in a neighborhood where a greater percentage of families have incomes below poverty level (9.6%v8.2%, $p<0.0001$), to be of Hispanic ethnicity (35%v2.6%, $p<0.0001$) or of Asian, American Indian, African American, Multiracial or Native Hawaiian/Pacific Islander descent ($p<0.0001$). Furthermore, LEP patients had more severe stroke scores (10v8, $p<0.0001$), more administration of tPA (13.1%v9.4%, $p=0.04$) and intra-arterial treatment (6.5%v4.3%, $p=0.008$), and less likely to ambulate independently at discharge (39.5%v51.4%, $p=0.003$).

The greater stroke severity among LEP patients, despite their comparable past medical history, indicate that LEP patients may have a higher threshold for stroke severity before deciding to go to the hospital. The reason for worse ambulatory status at discharge is unclear and may not be completely accounted for by initial stroke severity. Additional review of the data will be conducted to determine what variables impact ambulatory status.

**Characteristics of Patients at Boston Children's Hospital Experiencing Readmission
Within Ninety Days of Discharge from a Critical Care Setting**

Carlos Eduardo Estrada Alamo
Harvard Medical School, Walter Bradford Cannon Society, Class of 2017
Paul and Daisy Soros Fellow

Elliot Melendez, MD
Medicine Critical Care Program
Boston Children's Hospital

Nationally, there is increasing focus on hospital readmission rates as an indicator of quality of care. Thirty-day readmission rates range from approximately 5% for pediatric hospital discharges overall to up to 25% for children with complex care needs. For children with complex chronic conditions (CCC), dependence on medical technology assistance (TA) has been significantly associated with increased readmission rates. From January 1, 2012 to April 15, 2013, 239 patients were discharged directly home or transferred to an outside hospital (OSH) from the Boston Children's Hospital (BCH) Division of Medicine Critical Care (MCC) units. It is yet unclear which factors contribute to the risk of readmission in patients discharged directly from these units.

Our primary hypothesis is that patients discharged home from a BCH MCC unit with TA (i.e. gastrostomy, tracheostomy, cerebrospinal fluid ventricular shunt, or central venous vascular access) and a CCC experience a higher readmission rate compared to patients with a CCC in isolation or patients meeting neither criteria at discharge. Patients will be categorized into two clinical categories based on previous studies by Feudtner et. al. and TA, defined as a medical device used to maintain a patient's health status.

All patients discharged home or transferred to an OSH from a BCH MCC unit during the study period were screened. Chronic diagnosis prevalence and reasons for hospitalization were assessed. Demographic and clinical data was collected retrospectively. Admission and discharge data, including presence of invasive technologies, were obtained from medical chart review.

In this cohort, 72 patients (30.1% [n=72/239]) experienced at least one readmission within ninety days of an index discharge event. Ninety-day readmission rates were higher for patients meeting the CCC and/or TA criteria (45.9% [n=68/148] versus 4.4% [n=4/91]), CCC criteria (46.4% [n=58/125] versus 12.3% [n=14/114]), and TA criteria (48.3% [n=57/118] versus 12.4% [n=15/121]).

Patients with CCC and/or TA discharged from MCC units at BCH seem to have higher readmission rates than patients not requiring those resources. Further research is needed to explore additional factors that may influence readmission rates in this cohort. Research findings may result in the development of a strategy to identify and manage patients at high and low risk for early readmission. Reducing the rates of early readmission will ideally lead to improved overall care and may reduce overall health care costs.

A Pilot Group Visit Program for High Risk Pediatric Asthma Patients

Margaret O. Fallon, MEd
Harvard Medical School, Francis Weld Peabody Society, Class of 2017

Faye Holder-Niles, MD, MPH
Department of Medicine, Division of General Pediatrics
Boston Children's Hospital

Asthma is one of the most common chronic diseases of childhood and is one of the leading admission diagnoses at Boston Children's Hospital. Over 2,000 patients with asthma receive care at Boston Children's Primary Care at Longwood (CHPCC). Many of the patients are poor and live in inner city neighborhoods with high rates of ED visits and inpatient hospitalizations. Poor asthma outcomes are often related to fragmented care, social risk factors, poor knowledge of self-management, and family fatigue from caring for children with asthma. Further innovation is needed to improve outcomes in this vulnerable population.

Our objective is to develop and pilot an asthma group visit program for high-risk asthma patients at CHPCC. Our hypothesis is that these shared medical appointments will provide an innovative platform to deliver asthma education, while facilitating peer support for families who care for children with asthma. Additionally, these visits will help to enhance patient engagement with their healthcare team and will be a cost-effective tool to provide asthma care.

Our quality improvement project consists of three phases: 1) Patient engagement: 20 semi-structured parent interviews were conducted to solicit and incorporate family input into program development; 2) Curriculum development: parental feedback from the interviews was used to develop culturally and linguistically appropriate educational materials for paired patient and parent sessions; 3) Group visit implementation: 12-15 patient families are currently being recruited to participate in three group visits that will take place throughout the year.

Our preliminary results from the parent interviews revealed that 85% of families would be interested in participating in a group visit program. Families endorsed group visits as a way they could share experiences and learn from other families, while learning more about caring for their children with asthma. Families indicated that night or weekend sessions may help facilitate attendance and that the cost of parking could be an obstacle to attendance.

To assess the impact of group visit participation on asthma outcomes, we plan to assess changes in parents' knowledge, skills, and confidence in managing their children's asthma pre- and post-group visits utilizing the nationally validated Patient Activation Measure (PAM-13) assessment. ED and inpatient utilization rates post-intervention as compared to one year pre-intervention will also be analyzed.

Our pilot group visit program is part of an ongoing quality improvement initiative at CHPCC. Our results reflect the attitudes and opinions of our patient population and may not be broadly generalizable.

The Effect of a Novel Soluble Receptor on IL-13 Signaling and Metabolism**Ofer Fass****Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017****Richard T. Lee MD****Brigham and Women's Regenerative Medicine Center**

Interleukin-13 is a Th2-secreted cytokine with both physiological and pathophysiological roles. Most recently, IL-13 has been demonstrated to have an autocrine role in promoting skeletal muscle glucose metabolism, regulating hepatic glucose production, maintaining cell viability of pancreatic β -cells, and promoting beige fat thermogenesis. These results demonstrate a beneficial role for IL-13 signaling in improving glucose handling and systemic metabolic regulation, as well as mitigating the pathological processes of IL-13 dysregulation.

The aim of this study was to characterize the influence of a novel IL-13 soluble receptor (NSR) on IL-13 mediated signaling and effects. The initial hypothesis was that the NSR acts as a decoy receptor, blocking IL-13 signaling. In order to test this hypothesis, NSR was purified using an SF9 insect cell baculovirus expression system. Following purification, an *in vitro* A549 cell proliferation assay using tritiated thymidine incorporation was performed to determine whether NSR could inhibit IL-13 induced cell proliferation. Interestingly, NSR did not blunt IL-13-induced proliferation, rather enhanced proliferative effects. Furthermore, the NSR by itself demonstrated pro-proliferative activity. This is possibly due to NSR activation of proliferative pathways independent from that of IL-13.

In vitro studies were followed by *in vivo* analysis of NSR. C57/BL6 mice were given intraperitoneal injection of recombinant NSR. 24 hours post-injection, tissues were harvested for gene expression analysis. Analysis of hepatic tissue demonstrated an increase in expression of gluconeogenic genes PCX, PEPCK, and PPARG2A. This increase is consistent with our hypotheses, as previous studies have demonstrated that IL-13 knockout mice similarly demonstrate increased expression of gluconeogenic genes. Although the preliminary results are promising, more injections need to be performed to reach a higher degree of statistical confidence.

Future experiments will attempt to elucidate the mechanism of NSR on cell proliferation, as well as the physical interaction between NSR and IL-13. Additionally, elevated PPARG2A expression is of particular interest, as PPARG2A plays a role in beige fat thermogenesis. Therefore, it would be worthwhile analyzing adipose tissue for changes in thermogenesis gene expression.

**C-Reactive Protein for Diagnosis and Prognosis of Active Pulmonary Tuberculosis
in HIV-infected Adults in South Africa**

Joshua Foromera

Harvard Medical School, William Bosworth Castle Society, Class of 2017

Paul K. Drain, MD, MPH

Department of Infectious Diseases, Massachusetts General Hospital

Mycobacterium tuberculosis (TB) is the most common opportunistic infection among HIV-infected adults. Though treatable, TB is the leading cause of mortality among HIV-infected adults yet globally, less than 10% of the 33 million HIV-infected have been screened. South Africa is among countries that have the highest HIV/AIDS burden. Nearly 6 million South Africans, 18% of the adult population, are currently living with HIV. It is estimated that almost 90% of HIV infected adults will be infected with TB at least once and recurrent infections are common. More than half a million new cases of TB are diagnosed in South Africa annually, and upwards of 60% of those cases are among HIV positive adults.

TB testing and screening is necessary in HIV infected adults. Long delays in diagnosis, together with the elusive nature of HIV-associated TB have hampered progress in fighting HIV and TB co-infections in South Africa. Generally, sputum smear microscopy and radiographic imaging are used for diagnosis of TB and assessment of the effectiveness of TB treatment but atypical clinical manifestation and high prevalence of smear negative TB in HIV positive patients threaten the efficiency of these tools. This underscores the urgent need for inexpensive, non-invasive methods to diagnose TB and to estimate the effectiveness of TB treatment in HIV infected patients at the point of care.

In this study, we evaluate the utility of C-Reactive Protein (CRP) as a diagnostic and prognostic marker in HIV infected adults. We retrospectively analyzed data from 210 patients that was collected since June 2007. To be included in the original study, participants were over 18 years of age, had any 2 of 4 tuberculosis symptoms, (cough, fever, night sweats and weight loss) for more than two weeks. Upon enrollment, clinicians performed a physical examination and obtained a detailed social and medical history, and a venous blood sample. The data recorded included clinical signs/symptoms, laboratory test results and patients outcomes data.

We hypothesize that the levels of CRP will be very high in TB patients and that they will decrease as successful treatment progresses. However, the levels of CRP will remain high or may not decrease significantly in patients who do not respond to treatment. Similarly, we hypothesize that patients who remain with high levels of CRP during treatment have poor prognosis. Ultimately, we hope to use CRP levels as diagnostic and prognostic tools in HIV and TB infected adults.

A Cell Phone Based Patient Triage Program for Community Health Workers in Kenya: Key Challenges and the Importance of Strategic Partnerships for Success

Tiara M. Forsyth

Harvard Medical School, William Bosworth Castle Society, Class of 2017

Leo A. Celi, MD

**Critical Care Medicine, Beth Israel Deaconess Medical Center
Computational Physiology, Massachusetts Institute of Technology**

With over 4.5 billion cell phones in developing countries, mobile communication plays an increasingly fundamental role in global daily life. A recent study found that over 90% of Kenyans use a mobile phone and 20% report forgoing some normal expenditure (like a meal) to buy airtime. Kenya faces one of the world's greatest healthcare shortages with less than two physicians per 10,000 people. Many health centers have leveraged mobile phones to expand access to care (mHealth), but most implementations are small pilots with little monitoring or potential for scale-up.

Partners for Care (PFC), a Nairobi-based nonprofit, recognized the potential for mHealth in Kenya and worked to avoid mistakes made by previous implementers. In 2011, they began an mHealth program for patient triage serving 1000 households in the Marurui informal settlement. In collaboration with the US-based nonprofit Global HEED and Sana at Massachusetts Institute of Technology, they built an application using Sana's open-source mobile platform to help community health workers triage patients into 3 categories: referral to a health center, immediate hospital transfer, or point-of-triage care. They aimed to expand provider capacity in a community facing a healthcare staffing shortage and reach patients who may not otherwise seek treatment. In 2013, they expanded to a government-run rural health center serving an additional 3,000 households.

The goal of this SIM project was two-fold: (1) to evaluate PFC's mHealth program for effectiveness, efficiency, and potential for scale-up and (2) to negotiate a partnership with a local university to take over information technology management.

Our evaluation uncovered several key challenges, including limited internet connectivity and lack of technical literacy sufficient to troubleshoot software problems. Such challenges are common with technology-based innovations in resource-limited settings and were best overcome with adequate contingency planning, strong communication, and role flexibility among team members. We discovered that, in addition to their role administering the mHealth program, health workers serve as an important source of preventive care in the community, identifying household factors contributing to health issues and educating patients on health-promoting activities.

In July 2014, we successfully negotiated a partnership with Mount Kenya University for information technology management, transferring the role from US-based organizations. Local ownership will lead to improved sustainability through factors such as stronger institutional learning from successes and failures and long-term availability of software developers. Further, a clearer understanding of the local context and improved response time for technical issues guarantee a better product.

Development of a Computational, Objective Method for Segmenting PDL Fiber Regions

Jonathan E Foster

Harvard School of Dental Medicine, Oliver Wendell Holmes Society, Class of 2017

Gili Naveh, PhD, DMD

**Olsen Laboratory, Department of Developmental Biology
Harvard School of Dental Medicine**

Unlike bones, teeth have no self structural repair mechanism despite enduring high repetitive loads during daily use. The most important factor influencing tooth longevity is the ability of the tooth and its surrounding bone to dissipate stress during mastication. The periodontal ligament (PDL) is a soft tissue made of intricate collagen networks and other cellular and extra-cellular components. It connects the tooth to the jaw bone and is a main contributor to tooth movements and therefore crucial for tooth survival.

Despite the PDL's significance in tooth survival, its 3D structure is not fully understood. Past studies of the PDL structure have used 2D microscopy techniques, which require staining and sectioning of the samples, inherently altering the PDL structure. A recent study used microCT imaging to view in 3D the fresh, unstained, and un-sectioned PDL collagen fiber network of a rat molar. The collagenous network was found to be arranged in two densities: dense and sparse.

We utilized this method to image the PDL in a mandibular mouse molar. Since the pixel intensities of the tooth, PDL collagenous fibers and the bone overlap, the most accurate method of segmentation is manually, which is time consuming and highly subjective. In this study we aimed at creating an automated, computational method to segment the PDL fibers as well as identifying the sparse and dense fiber regions in an objective manner.

Given the overlap of pixel intensity between the PDL, tooth, and bone, existing intensity-based segmentation tools were inadequate. We therefore utilized pattern and shape-based features of the image for segmentation. The images were filtered and the hard tissues were removed using a relationship between pixel values and their spatial variation. The PDL fibers were segmented by identifying areas containing a large variation in pixel values, an inherent feature of the PDL compared to other soft tissue in the image. Finally the volumetric density of the fibers throughout the PDL was calculated.

This automated process resulted in a large reduction in time-consumption compared to manual segmentation as well as reducing user input to decrease subjectivity. The density calculation objectively identified the sparse and dense fiber networks within the segmented PDL. We analyzed the resulting segmented PDL images and identified sparse and dense fiber regions, correlating to the results from the rat model.

The presented automated method enables us to perform efficient, consistent and objective analyses of the PDL 3D structure.

Assessing Patient Satisfaction with the MGH Medicare 3-Night Rule Waiver**Anna E. Frackman****Harvard Medical School, Walter Bradford Cannon Society, Class of 2017****Ryan W. Thompson, MD****MGH Integrated Care Management Program, Department of Medicine
Massachusetts General Hospital**

Patient satisfaction with healthcare delivery has long been known to be robustly associated with compliance with suggested interventions (Hulka et al 1976, Uhlman et al 1984) as well as favorable clinical outcomes (Alazri and Neal 2003). Given this information, patient satisfaction is a very important area to be aware of when making any type of policy change affecting the way that care is delivered.

Currently, according to Medicare guidelines, a beneficiary must be an inpatient in a hospital for at least three nights prior to being discharged to a skilled nursing facility (SNF) (Lipsitz 2013). While the rule was designed to prevent or reduce overuse of SNFs, it also potentially creates an incentive to hospitalize patients who could have been discharged or do not need to be hospital inpatients but do need the round-the-clock care available in SNFs (Birmingham 2008). In July of 2010, the Massachusetts General Hospital (MGH) received permission to waive this requirement for a subset of high-risk patients in a pilot study of direct-to-SNF admissions. Largely on the strength of the data from the MGH pilot study, the Centers for Medicare and Medicaid Innovation (CMMI) have expanded the waiver program to one that any of the Pioneer ACO programs can apply for. Pilot data indicate that a waiver of the three-day rule for Medicare beneficiaries may represent a way to decrease costs and stress on the medical system without sacrificing quality of care.

It is important to assess whether this method provides care that results in patient satisfaction equal to or greater than satisfaction with care under the original rules. To this end, I created and am in the process of validating a tool for assessing satisfaction.

Initially, I went through a series of key informant interviews in order to identify important domains of inquiry. These included: coordination between MGH and the SNF, Shared decision making and patient understanding of care planning, Satisfaction, and Errors. I then used these inputs and validated questioning tools to create a draft survey tool.

In order to validate the questionnaire, I am currently using an iterative process of cognitive interviewing, a technique standardly used to improve the relevance and comprehension of new survey questions in the relevant patient populations (Bredart et al 2014). Through this process, we can determine whether patients understand the questions and can identify potential response errors and errors in question interpretation.

Simultaneous neuronal and spatial characterization of rodent learning**Gabriel N. Friedman****Harvard Medical School, Walter Bradford Cannon Society, Class of 2017****Ziv Williams, MD****Center for Nervous System Repair, Department of Neurosurgery
Massachusetts General Hospital**

Studies of rodent behavior have yielded tremendous insights into the neural activity associated with learning. A present limitation to understanding rodent learning is the challenge of matching single-neuron recordings via implanted microelectrodes with the physical location of a rodent throughout the duration of a given learning paradigm. While existing experimental techniques are capable of recording high-fidelity neuronal signals during learning via microelectrodes, position information would enable valuable and intriguing insights into the nature of brain activity during all phases of learning.

The present study seeks to develop methods to study patterns of neuronal activity throughout the different phases of learning acquisition in both the rodent agranular insular (AI) and cingulate (Cg) cortices, through the implantation of 2 16-channel MicroProbes microelectrodes arrays into a single mouse. Additionally, we will seek to determine whether this biophysical information can be correlated with rodent spatial location in a T-maze learning task to understand various patterns of neural activity at each stage of the learning process.

In this study, C57BL/6 were trained to associate either the left or right goal-arm of a T-maze with a food pellet reward. During a given block, only one goal-arm was baited with food reward, and 60 trials were performed in each block. Three blocks were performed each day for each mouse. We measured mouse accuracy by calculating the number of times it selected the rewarded goal-arm of the T-maze divided by the total number of trials completed. Location data was tracked via a machine-learning algorithm, which produced x- and y-coordinate data for each frame of video recorded during the learning paradigm. This data could then be aligned with output from two microelectrode arrays that were implanted in the AI and Cg cortices. A particular focus of this experiment is dedicated to understanding the process of extinction learning and reversals at the beginning of each block, in which a mouse must unlearn the previous direction that it had been taught.

This experiment is still in the data-collection phase, so results will be forthcoming.

Beyond the Emergency Obstetric and Neonatal Care Trial: A Qualitative Look at the Content, Delivery and Impact of the Community Mobilization Component of the EmONC Trial in Nagpur, India

Laurel S. Gabler, MSc, PhD
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Patricia L. Hibberd, MD, PhD
Division of Global Health, Department of Pediatrics
Massachusetts General Hospital for Children

In many countries a high percentage of women still die during childbirth, and many children do not survive past the neonatal period. The NIH-funded Emergency Obstetric and Neonatal Care (EmONC) trial was a multi-site randomized control trial aimed at reducing maternal and neonatal mortality and morbidity by improving access to quality services. In order to achieve this goal, community facilitators in intervention groups received trainings on approaches for increasing local engagement with these issues. These facilitators were then responsible for carrying out phase-wise meetings with local stakeholders to help them strategize about how to address their communities most pressing maternal and neonatal health concerns.

Nagpur, a city in central India, was the most active of the trial sites. Although no statistically significant improvements in mortality and morbidity were observed in any of the trial sites, Nagpur serves as an excellent foundation for understanding the broader role of community mobilization in health behavior. To that end, this study used a combination of existing qualitative meeting data and data collected through informal discussion groups with community facilitators and health workers in both study and control clusters to take a more nuanced look at the community mobilization component of the EmONC trial, and to understand whether or not these trainings and meetings impacted community engagement.

In Nagpur, 11,494 meetings were held and 211 follow-up plans were devised to address the most pressing maternal and neonatal health concerns in each of the clusters. The major maternal problems prioritized by the communities were postpartum and antepartum hemorrhage, pre-eclampsia/eclapmsia and obstructed labor, while the major neonatal problems prioritized were respiratory problems, seizures, and low birth-weight. The majority of communities felt that financial, educational and cultural barriers were the primary barriers to improving conditions, and that increased community savings, improved earlier recognition of problems through education and provision of emergency transportation were key tactics to decreasing mortality.

In comparing community members who participated in the trainings to those who did not, those who participated appeared more involved with their communities and more capable of strategizing about how to tackle current problems even 3 years after the trial conclusion. More, many of those who participated felt that they had gained confidence to rally their communities to effect change. These preliminary results indicate that while the trial may not have resulted in quantitative improvements, it likely impacted the level of engagement of those who participated. It is therefore critical to look beyond the quantitative results and explore these community meetings and their impacts more qualitatively.

Circulation:

Six Short Stories about Encounters between Strangers in the World of Medicine

Carolyn Gaebler

Harvard Medical School, William Bosworth Castle Society, Class of 2017

Bret Anthony Johnston

Harvard University

English Department

Background: Stories about the healthcare—stories patients tell in our first-year clinics, articles about Obamacare, anecdotes from our own families—often pivot on the strangeness of navigating between extremes of intimacy and anonymity. To what extent is empathy like or unlike an orange? To what extent do we set healing apart from commodity?

Medicine, as a collection of empirical disciplines, may not be able to articulate this problem of intimacy and anonymity from inside itself. We may need to engage other, imaginative practices to describe and grapple with it.

Methods: During my first year at HMS and the summer following, I wrote a collection of short stories about encounters between strangers in the world of medicine. The collection, *Circulation*, includes stories about blood donation, medical debt, talismans and commodities, rituals of healing, humor (in both senses of the word), and gross anatomy.

The stories, in order, are called “Blood,” “Money,” “Art,” “Hands,” “Spleen,” and “Anatomy Dreams.” Each story stands alone, but the six are connected. They share characters and objects. I have always been interested in the fiction of economies, and this work reflects on economies of stories and bodies.

I hope that these stories are interesting to people with particularly rich or extensive experience with the world of medicine—patients, doctors, and other providers—but I also hope that they are interesting to a broader audience. I am interested in the ways in which medicine is at once set apart from and very much embedded in other webs of representation and exchange.

Limitations: I do believe that imagination and empathy are closely linked, but I am hesitant to make claims about the instrumental value of fiction. My project explores a “problem,” but does not necessarily represent a “solution.”

Conclusion: The first story from the collection, “Blood,” was published in the May issue of *Hello Mr.* The five remaining stories are under consideration at other magazines. I am grateful for the chance to devote my summer months to editing and writing. The opportunity helped me grow as a writer and allowed me to reflect on how fiction might fit into a medical career.

**Upper Airway Length is Predictive of Obstructive Sleep Apnea in Syndromic
Craniosynostosis**

Karan P. Ganjawalla

Harvard School of Dental Medicine, William Bosworth Castle Society, Class of 2017

Bonnie L Padwa, DMD, MD

**Department of Plastic & Oral Surgery, Boston Children's Hospital
Harvard Medical School**

Midfacial hypoplasia is a characteristic feature of the syndromic craniosynostoses and predisposes these patients to developing obstructive sleep apnea (OSA). The purpose of this study is to characterize anatomic factors that could explain airway obstruction in these disorders.

This was a retrospective cohort study of 50 patients with syndromic craniosynostosis treated at Boston Children's Hospital between 2000 and 2014. Predictor variables were: patient age, gender, BMI, syndromic diagnosis, and parameters of upper airway length and size measured on lateral cephalograms. To control for age, upper airway length was corrected for differences in patient height. Subjects with a diagnosis of OSA, confirmed by overnight attended polysomnography, were compared to patients who had no OSA on polysomnography or no history of sleep disordered breathing. Descriptive, bivariate, and regression statistics were computed. For all analyses, $p < 0.05$ was considered statistically significant.

Patients with or without OSA did not differ significantly in age, gender, BMI, or syndromic diagnosis. Non-parametric comparisons revealed that patients with OSA had increased upper airway length ($p=0.016$), decreased posterior airway space ($p=0.001$), and more severe midfacial retrusion ($p=0.022$) as compared to patients without OSA. The adjusted odds ratio for OSA was 32.91 in patients with an upper airway length greater than 45.33 mm per meter height ($p=0.02$), and for every 1 mm decrease in posterior airway space, the risk of OSA increased by 30%.

Patients with syndromic craniosynostosis and OSA have a longer upper airway, smaller posterior airway space, and more severe midfacial retrusion than those without OSA.

Idiopathic bone cavity of the jaw: a case series**Ricardo Garza Jr****Harvard School of Dental Medicine, Walter Bradford Cannon Society, Class of 2017****Cory Resnick, DMD, MD****Department of Plastic and Oral Surgery****Boston Children's Hospital**

Idiopathic bone cavities (IBCs) are benign intraosseous lesions of unknown etiology. They most often occur in long bones but can also be found in the maxillofacial skeleton. There is no standardized treatment algorithm for this lesion, and its pathogenesis is poorly understood. Failure to include this lesion in the differential diagnosis may lead to unnecessarily invasive diagnostic and treatment interventions.

We aim to describe the demographics, clinical and radiographic presentations, and treatment outcomes for a series of patients with IBCs that were diagnosed and treated by exploration and curettage.

This is a retrospective consecutive series of patients evaluated for IBCs at Boston Children's Hospital from 2000-2014. Potential subjects were identified by evaluation of the oral pathology database for the Department of Plastic and Oral Surgery. Inclusion criteria included patients who underwent exploration procedures that were consistent with an IBC, and the availability of a complete medical record. Exclusion criteria included an alternative diagnosis and patients with more extensive osseous abnormalities such as fibrous dysplasia. The diagnostic exploration procedure which was employed when an IBC was included on the differential diagnosis involved creation of a neck-of-tooth incision and elevation of a mucoperiosteal flap, followed by creation of a small corticotomy and exploration of the wound cavity. If a solid lesion was encountered or a soft-tissue lining was identified, these were sent for biopsy. If neither solid contents nor cystic lining were seen, this was considered diagnostic of an IBC. In those cases, all bony walls were curetted and the wound was closed, and the procedure was considered both diagnostic and therapeutic. Predictor variables for this study included demographics, medical history, clinical presentation, and radiographic lesion size and appearance. Outcome variables included need for additional management of this lesion after the initial exploration and curettage and radiographic bone fill of the lesion cavity. Descriptive statistics were calculated for these variables.

Twenty-six patients with IBCs were included. The mean age at presentation was 12.8 years (range 9 – 16) and the mean time from initial presentation to diagnosis was 3.4 months (range 0 – 41.3). All lesions were located in the mandible, with 11 in the anterior mandible, 10 in the mandibular left quadrant, and 5 in the mandibular right quadrant. Aspiration of the wound cavity was performed in 5 patients prior to biopsy, and the aspirates demonstrated absence of malignant cells. Of the 4 patients who had post-operative imaging, radiographic bone fill was seen in 3 (75%). Two of the twenty-six patients had biopsies repeated, but tissue samples sent for pathology were consistent with diagnosis of IBC.

Based on our preliminary analysis, a simple wound exploration and curettage procedure is sufficient for diagnosis and treatment of suspected IBCs. Because 45% of our patients were referred prior to the initiation of orthodontic treatment, we aim to obtain post-orthodontic treatment radiographs for these patients in the future to better characterize any radiographic changes observed in the lesion.

Isolating and Characterizing a Novel Population of Meniscal Stem/Progenitor Cells**Ashira E. Gendelman****Harvard School of Dental Medicine, William Bosworth Castle Society, Class of 2017****Laura Gamer PhD & Vicki Rosen PhD
Department of Developmental Biology
Harvard School of Dental Medicine**

Meniscal injuries are the most common knee injuries, yet current meniscal repair efforts are largely unsuccessful and cannot prevent the degenerative changes that result in osteoarthritis (OA). One attractive option for expanding treatment options for meniscal injury is regenerative cell therapy. Already, stem/progenitor cells have been identified and characterized in numerous adult musculoskeletal tissues, however no studies to date have identified a definitive population of meniscus stem/progenitor cells (MSPCs).

Isolating and characterizing a reparative population of stem cells resident in the adult meniscus is the next crucial step towards developing a regenerative cell therapy for meniscal injury and the prevention of osteoarthritis. We hypothesize that the adult meniscus harbors a cell population that exhibits stem cell characteristics, and that those stem cell characteristics change as a function of age.

In order to isolate MSPCs, menisci from 8-week and 6-month-old tomato mice were microdissected out and incubated for one week in primary cell culture. The colony morphology of MSPCs was examined using Hoechst stain and fluorescent microscopy. MSPCs from 8-week and 6-month-old mice were then compared for differential gene expression of meniscal and stem cell markers using qPCR and $\Delta\Delta CT$ analysis method.

The following findings were observed. MSPCs were visible in meniscal primary culture after roughly 8 days post dissection. Fluorescent microscopy revealed that the MSPCs expressed tomato. Gene expression analysis revealed that MSPCs derived from the younger 8-week-old mice demonstrated elevated gene expression of meniscal markers *BMP2* and *Col2*, as well as elevated expression of stem cell markers *CD45*, *CD44*, and *CD29* compared to the MSPCs from the older, 6-month-old mice.

Our preliminary examination of the MSPCs indicates that there does appear to be a population of cells residing within the meniscus of the knee that can migrate out of the meniscus, grow in colonies, and express a gene profile consistent with stem/progenitor cells. Additionally, MSPCs derived from younger mice appeared to have greater expression of stem-cell markers than MSPCs derived from older mice.

Our comparison study of MSPCs derived from three different age groups of mice (8wk, 6month, and 1 year) will be completed later this year, as our “56-week-old mice” will not become of-age until October 2014. This year we plan to further investigate the 1) gene expression profiling patterns, 2) migratory capacity, 3) self-renewal capacity, and 4) multipotency of this novel population of meniscal cells.

The acceptability and impact of a weekly SMS program to support antiretroviral therapy adherence in KwaZulu-Natal, South Africa

Nathan T. Georgette

Harvard Medical School, Francis Weld Peabody Society, Class of 2017

Jessica E. Haberer, MD, MS

Assistant Professor of Medicine

Massachusetts General Hospital & Harvard Medical School

Effective antiretroviral therapy (ART) for HIV infection requires persistently high levels of adherence. Prior studies have demonstrated that weekly supportive short message service (SMS) text messages can improve adherence to ART, although not in all settings.

A clinical program of weekly SMS messages was launched at a government HIV clinic near Durban, South Africa in September 2013. All patients taking ART who had a cell phone number on file were enrolled in an opt-out manner. This program was modeled after those shown to improve ART adherence but was implemented in the context of routine care, thus offering a unique opportunity to understand the impact of SMS messages. We investigated the patients' perceptions and acceptance of the SMS program, as well as their adherence to ART over time.

Perceptions and acceptability were assessed using individual structured interviews among adult patients who were enrolled in the program at its launch. Interviews were conducted in either Zulu or English and asked about cell phone usage and experience with the clinic program. To assess adherence to ART, we conducted a retrospective cohort study of pharmacy refill patterns. Approximately 50% of adult patients did not initially have a valid cell phone number recorded and thus could not participate in the SMS program; these patients were designated as the comparison group.

To date, 79 of a planned 100 individuals have been interviewed; data collection is ongoing. A total of 69 (87%) received at least one SMS from the program, of whom 63 (91%) would recommend the program to a friend and 68 (99%) stated that the SMS help them remember their medication. One (1%) patient reported feeling that the SMS violated their privacy. An initial t-test on the retrospective cohort of 2216 adults patients found mean adherence declines of 4.5% and 6.1% over time in the SMS and comparison groups, respectively ($P=0.054$). We plan to use generalized estimating equation regressions to further analyze the cohort data with other predictors (e.g. age, gender, CD4 count).

Based on the preliminary results, the SMS program appears to be well accepted by patients with little report of social harms. However, the interview responses may be subject to response bias and non-participation of patients who do not like the program. While our findings may also be limited by unmeasured confounders, they provide a valuable assessment of the potential for SMS to improve ART adherence in routine clinical care in South Africa.

The Risk of Tuberculosis Infection in U.S. Army Soldiers During Deployment**Mia E. Geurts****Harvard Medical School, Francis Weld Peabody Society, Class of 2017****James Mancuso, MD, MPH, DrPH, LTC, MC, USA
Department of Preventive Medicine and Biometrics
Uniformed Services University of the Health Sciences**

Members of the U.S. Military are generally at low risk for tuberculosis (TB) infection. Although studies have found no association with TB disease and deployment, individual cases have been reported which are attributable to deployment to tuberculosis-endemic areas such as Iraq and Afghanistan. Additionally, the incidence of latent tuberculosis infection (LTBI) associated with military deployment is unknown. Previous studies have estimated it to be between 0.1% and 10%. The objective of this study was to determine the overall incidence of LTBI with service in the U.S. Army and the incidence resulting from deployment.

We performed a retrospective cohort study using follow-up data from a previous study at Fort Jackson in 2009. Soldiers with no LTBI at time of accession into the military were assessed for new incidence of LTBI from 2009 to May 2014.

1,733 soldiers of the original 1,978 from the 2009 study were free of LTBI at time of accession and had follow-up data available. The incidence of LTBI infection associated with deployment was estimated as 0.5%. We found no new cases of LTBI associated with other military service. We observed no association between military occupational specialty and LTBI.

The risk of LTBI during military deployment and other military service is low, but focal risks do exist. These findings support current Department of Defense and Center for Disease Control guidelines for targeted testing. Our estimate is lower than previous studies of LTBI in long-term travelers, which have suggested an average risk of 2% or greater. We believe that our study more carefully assessed/mitigated important potential confounders such as a baseline prevalence of LTBI in the study population, the effects of boosting, cross reactions due to non-tuberculosis mycobacteria, and occupational exposures. Our study is somewhat limited by a low number of positive LTBI cases, reducing our statistical power. Our study has limited generalizability to non-military populations.

**Linkage Intervention for HIV Care: Enhanced Communication Tools
Uganda Nakivale Refugee Settlement**

**Kelsy Greenwald
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017**

**Kelli O’Laughlin, MD, MPH
Emergency Medicine Department, Brigham and Women’s Hospital
Medical Practice Evaluation Center, Massachusetts General Hospital**

According to the WHO, Sub-Saharan Africa accounts for 71% of global AIDS deaths. Refugees, 2.8 million of whom live in Sub-Saharan Africa, are particularly susceptible to infections. Refugees at the Nakivale Refugee Settlement are offered free HIV tests and medication. However, previous studies have shown that there is poor linkage to care after positive testing.

This study explores the use of an enhanced communication intervention to lower barriers to linkage to HIV care. For example, phone calls and text messages can be used to encourage testing, deliver information, and remind patients about follow up appointments. A control group of HIV-infected refugees will be compared to an intervention group, who will be given a reminder phone call and text message once a week if they are not going to clinic, and once a month if they are going to clinic. After six months, further data will be collected from both groups on whether the refugees were able to be linked to care, their perception on the intervention technique, and other ideas they have for interventions.

The seven weeks in Uganda were spent designing the program:

- 1) Meeting with partners: Medical Teams International (MTI) who runs the health programs at the Nakivale Refugee Settlement; UNHCR; and the Community Advisory Board (a group of representatives from different countries present in the Settlement – Democratic Republic of the Congo, Somalia, Rwanda, and Burundi).
- 2) Creating the tools necessary to gather data – operations manual; phone call and text message scripts; timelines and flow diagrams; phone call collection database.
- 3) Aiding in the training and hiring of participants involved in data collection.

Data collection will continue over the next 12 months. This will be done by research assistants present at the site, and done in four separate languages: Kinyarwanda, Kiswahili, Runyankore, and English.

Certain limitations involved in the study included finding tools and scripts that would be appropriate and useful for all cultures involved; completing aspects of the project development with limited internet and electricity; and meeting with individuals from our partner organizations who were frequently absent from the site. Additional limitations included the need to keep the same context as the control for the new intervention cohort, such as not adding Somali-translated forms to increase the levels of participation from a typically low-participant group or using a more in-depth demographic questionnaire to see if other factors in a patient’s history affect his access to care.

Maternal and paternal height and sex-specific, offspring height development from second trimester to mid-childhood

Emily A. Gross

Harvard Medical School, William Bosworth Castle Society, Class of 2017

Matthew W. Gillman, MD, SM

**Obesity Prevention Program, Department of Population Medicine
Harvard Medical School**

Height is associated with varied social and health outcomes, including income, mate preference, cancer risk, and cardiovascular and respiratory disease mortality. Height development is assessed starting in utero via fetal femur length. Adult height is highly heritable (80-90%) and studies show associations between maternal height and offspring length as early as the 2nd trimester. However, most studies look at static linear measures or restrict their analysis to the prenatal or postnatal period, failing to capture the dynamicity of height development. Our analysis examined the association of maternal and paternal height with length/height changes beginning in utero and extending through mid-childhood.

We analyzed data from 1424 participants in Project Viva, a prospective cohort study of pregnant women and their children. Outcomes were offspring length/height expressed as z-scores, including femur length from 2nd trimester ultrasound, birth and 6 month length, and 3 and 7 year height. To assess linear growth, we created change variables (i.e. birth length z-score – femur length z-score), and analyzed their association with maternal and paternal height using a linear mixed model. Sex-stratified analysis was performed.

Regression analysis showed that for every one z-score increment in maternal height, length z-score was 0.17 (95% CI, 0.10, 0.24) higher from 2nd trimester to birth, 0.10 (0.05, 0.15) from birth to 6 months, 0.15 (0.11, 0.19) from 6 months to 3 years, and 0.08 (0.04, 0.12) from 3 years to 7 years. Corresponding z-score increases per z-score increment in paternal height were 0.14 (0.08, 0.21), 0.12 (0.07, 0.17), 0.12 (0.08, 0.17), and 0.07 (0.03, 0.11). Results were unchanged when adjusted for the other parent's height or sociodemographic factors. Differences between male and female offspring existed from birth to 6 months, with one maternal height z-score increment giving a 0.13 (0.03, 0.23) increase in male length z-score but -0.01 (-0.12, 0.11) in females. Early childhood disparities included a one z-score increment in paternal height increasing 6 month to 3 year z-score in females 0.12 (0.01, 0.23) and 3 to 7 year z-score 0.21 (0.11, 0.31), while in males the increase was only 0.06 (-0.04, 0.17) and 0.15 (0.04, 0.26) for corresponding intervals.

Maternal height has a stronger positive association with length change prenatally, suggesting mother's height may have additional non-genetic influences on the in utero growth environment. This association is reversed from birth through infancy. Differences in parental height associations with female versus male length changes suggest different, sex-specific mechanisms underlie linear growth.

Determining the role of native amelogenin P173 and its cleavage product P148 in the transformation of amorphous calcium phosphate in enamel biomineralization

David Gu

Harvard School of Dental Medicine, Walter Bradford Cannon Society, Class of 2017

Henry C. Margolis, PhD

**Center for Biomineralization, Department of Applied Oral Health Sciences
The Forsyth Institute**

Amelogenesis is a highly regulated process responsible for the formation of dental enamel. Dental enamel is the hardest substance in the human body due to its unique mineral organization and composition (over 95% mineral by weight). The presence of two proteases at different stages of amelogenesis has been identified as being crucial for proper enamel formation. In the secretory stage, proteins, primarily amelogenin, are secreted by ameloblasts to form the enamel matrix. Amelogenin is then selectively cleaved by matrix metalloproteinase-20 (MMP-20) during this stage. During the maturation stage, enamel matrix proteins are almost completely degraded by serine protease kallikrein-4 (KLK4) and replaced by mineral to achieve the highly mineralized hierarchical enamel structure.

The purpose of this study is to further investigate the roles native full-length amelogenin (P173) and its predominant secretory stage cleavage product (P148) play in amelogenesis. We have hypothesized that the transformation of the initially formed amorphous calcium phosphate (ACP) to ordered hydroxyapatite (HA) crystals is uniquely brought about by MMP-20. We further hypothesize that P148 plays the key role of preventing unwanted mineral formation, while P173 has the structural capacity to guide the formation of ordered bundles of enamel crystals.

We examined the cooperative influence of KLK4 on the effect full-length P173 and truncated P148 has on spontaneous calcium phosphate mineralization *in vitro*. Protein degradation was assessed by gel electrophoresis, while effects on mineralization were analyzed using transmission electron microscopy (TEM) and selected area electron diffraction, as a function of time.

We found that KLK4 effectively degraded P173, but not P148 under our experimental conditions and kinetics. This finding may be related to known differences in the self-assembling behavior of these amelogenins. Nevertheless, we had expected the presumably less selective KLK4 would also degrade P148. Hence, further experiments are needed under modified experimental conditions. Consistent with our findings on protein degradation, however, TEM analyses showed that P173 degradation by KLK4 induces ACP transformation to form needle-like HA crystals, while ACP transformation was not observed using P148 under the same experimental conditions.

To date, these data suggest that P173 and P148 may play different roles in the process of amelogenesis. However, further experiments are needed to more firmly establish KLK4's potential role in regulating amelogenin-mediated mineral formation. Additionally, further mineralization experiments are needed to assess differences in the effects of MMP-20 and KLK4 on P173 degradation and mineral formation *in vitro*.

**Healthcare Models that Address Access to Specialty Care in
Rural Resource-Poor Settings: A Systematic Review**

José Omar Gutiérrez

Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Jennifer Kasper, MD, MPH

**Division of Global Health, Department of Pediatrics
Massachusetts General Hospital for Children**

Shortage of health care providers (physicians, nurses, and midwives), facilities, and distances between providers can make access difficult for rural communities. This is especially true when considering specialty care, which decreases as locations become smaller and/or isolated. While organizations are making an effort to reach these communities and increase access to specialty care, they are either not documented or have not been covered in a collective effort. I sought to provide an overview by conducting a systematic review of the different models that have been implemented in resource-poor settings with a focus on rural areas. Additionally, I plan to highlight findings from my independent analysis on a model in rural El Salvador, which has not yet been described in scientific literature.

An extensive literature search was conducted using the following text search terms: specialty care, resource-poor, resource limited, rural, and sub-specialty care, surgery, cancer care. A secondary search of Google using specific phrase combinations was also conducted. Additionally, references of selected articles for the review were scanned for similar articles pertaining to the research question. In total, 51 articles were identified to meet the criteria to be included in this review.

To date, only a fraction of the total articles collected have been analyzed and summarized for the review. The current data highlights three common themes: finance, human capital, and logistics. Different models developed innovative ways to finance specialty care or subsidize different components in the delivery process. Others focused on human capital by either electing to bring foreigners through mission work, task shifting, or using telecommunication. Lastly, most of them identified ways to better organize how, when and where the care was delivered.

My preliminary findings emphasize the complexity of addressing access in these regions. There is no model that is comprehensive. However, because each model focuses on one or a few components, all of which are equally important, the collective is informative. Currently, it appears essential for all three themes need to be addressed in order for a model to be effective at reaching these underserved areas.

The second aim of this project was to incorporate a qualitative data analysis from a novel healthcare model in El Salvador that was being led by a colleague at HMS. We did not anticipate and allocate enough time to transcribe and translate the Spanish interviews. As a result, we have set back our timeline for coding and qualitative analysis significantly.

Conformational Dynamics of Antibodies via *in silico* Simulations**Alexander Steven Hahn****Harvard School of Dental Medicine, Walter Bradford Cannon Society, Class of 2017****Piotr Sliz, PhD****Department of Biological Chemistry and Molecular Pharmacology
Harvard Medical School, SB Grid**

A fragment antigen-binding (FAB) domain is the region on an antibody that specifically binds to antigens (the two tips of the “Y” in each antibody). Most FABs are readily crystallizable and their amino acid sequence is easily determined via X-ray crystallography. However, the phase and, therefore, the 3-dimensional structure of the protein is difficult to obtain from the diffraction pattern. As a result, understanding the conformational dynamics of the protein can help elucidate its structure without extracting a phase from the diffraction pattern.

Given the number of proteins which have their structures already solved, overall, the “linker” regions connecting the variable and constant domains of each FAB exhibit the greatest flexibility in determining distinct conformational states. Consequently, the angle formed between the variable and constant domains, known as the elbow angle, was used as the main quantitative measure to differentiate conformational states in simulation.

Simulations were prepared using molecular modeling software and carried out on the “GOLDFINGER” and “ORCHESTRA” supercomputing clusters, maintained by SB Grid and Harvard Medical School I.T., respectively. 10, 1 micro-second protein simulations, requiring an aggregate ~25000 hours of CPU processing, finished in about 2 months when run simultaneously on high-end GPUs. All proteins were solvated in a cubic, water box under physiological conditions (i.e. pH = 7.4, Temperature = 300K, etc.).

Crystal structures in the protein data bank reveal a wide range of elbow angles from 140 to 220 degrees. However, simulations revealed that FABs favor lower elbow angle conformations in solution, regardless of crystal, initial elbow angle. This is due to a set of conserved residues between the domains which form a strong hydrogen bonding network. As a result, although the protein data bank displays FABs of a wide variety of elbow angles, simulations reveal that they should all relax to an elbow angle range of 140 to 160 degrees.

Overall, FABs are quite rigid and, regardless of the crystal structure, ultimately relax into a lower elbow angle between 140 to 160 degrees in solution.

Designing and Testing a Dendritic Cell Targeted Vaccine for Basal Cell Carcinoma in Mice**Karyn A. Haitz****Harvard Medical School, Walter Bradford Cannon Society, Class of 2017****Niroshana Anandasabapathy, MD PhD****Anandasabapathy Lab, Department of Dermatology
Brigham and Women's Hospital**

Basal cell carcinomas (BCC) comprise 80% of skin cancer and are the most frequent of all cancers. Developing a vaccine against BCC could reduce high treatment costs and greatly improve quality of life for patients with Basal Cell Nevus Syndrome, a genetic disorder leading to hundreds to thousands of BCC lesions in a lifetime and frequent scarring surgical procedures. BCC is commonly generated by Hedgehog signaling pathway mutations, most often due to mutational inactivation of the tumor suppressor gene Patched 1 (Ptch1). Hedgehog interacting protein 1 (HHIP1) is a hedgehog target overexpressed in BCC and DEC205 is a dendritic cell (DC) antigen uptake receptor highly prevalent among skin resident DCs.

The objective of this study is to generate a fusion construct of anti-DEC205 and HHIP1 and purify the fusion protein for use as a DC targeted vaccine to the immunogenic epitopes of HHIP1 for BCC prevention in a mouse model of UV-induced BCC.

DNA coding the pPT27 domain of HHIP1 (aa147-483) was PCR amplified from pRSETb vector and ligated with DNA coding the anti-DEC205 heavy chain or IgG control. Ligation products were gel extracted, transformed into bacteria, and purified for mammalian cell protein expression. The fusion antibody was expressed by transient transfection in HEK293 Freestyle cells and purified on protein G columns. Protein characterization and functional testing were performed using Western blot and fluorescent-associated cell sorting (FACS) staining.

Purified anti-DEC205-HHIP1 was characterized by SDS-PAGE and Western blot at ~230kD as expected using goat anti-mouse IgG (H+L)-AP. Specific binding was verified by FACS staining on CHO cells stably transfected with mouse DEC205 receptor using goat anti-mouse IgG-FITC. Prime-boost immunization of wildtype mice is being performed to validate that the fusion construct elicits an immune response. Vaccine will then be given to Ptch +/- K14-Cre-ER p53 fl/fl mice, a UV-induced BCC model, at staggered doses. Assays for cellular and humoral response will be performed and analyzed on all mice and BCC tumor number, area, and burden will be assessed for BCC-inducible mice. For antigen challenge assays I have designed a peptide library based on pPT27 and non-pPT27 HHIP1 controls.

These data show that an anti-DEC205-HHIP1 fusion antibody can be generated, has adequate solubility for secretion by mammalian cells, and can functionally bind to DEC205 target receptor in vitro. Further research will be conducted to determine the efficacy of this product as a vaccine against BCC in vivo in mice.

Generation of Novel Murine Models of Acute Myeloid Leukemia Using CRISPR/Cas9 Genome Editing to Characterize Therapeutic Response**Saurav Daniel Haldar****Harvard Medical School, Irving M. London Society (HST), Class of 2017
St. Baldrick's Foundation Summer Fellowship****Benjamin L. Ebert, MD, PhD
Department of Hematology
Brigham and Women's Hospital**

Acute myeloid leukemia (AML) is a hematological malignancy that remains a challenge to treat in the clinic because it exhibits profound heterogeneity in both its molecular genetic landscape and its response to currently available therapies. To dissect the relationship between the genetic lesions driving AML and the differential prognoses observed in patients, there is a critical need for the generation of animal models that reflect the heterogeneous nature of AML as a disease. Historically, efforts to this end have been plagued by technical limitations in the ability to introduce multiple co-mutations into a single model system. With the recent advent of CRISPR/Cas9 genome editing, many of the pitfalls previously associated with modeling the genetic complexity of AML *in vivo* have been overcome.

In this study, we sought to generate two novel murine models of AML with combinatorial genetic lesions engineered by CRISPR/Cas9 to gain further insight into therapeutic response and resistance. Based on analysis of patient genotypes, we hypothesized that a murine model with *Tet2*, *Runx1*, *Ezh2*, and *Nras* mutations would exhibit a secondary AML phenotype that is less responsive to therapy, while a murine model with *Tet2*, *Npm1*, *Dnmt3a*, and *Flt3* mutations would exhibit a *de novo* phenotype that is more responsive to therapy.

Bone marrow harvested from *Tet2*^{-/-} donor mice (*n* = 5) was subject to c-Kit enrichment to select for hematopoietic stem and progenitor cells (HSPCs). The *Tet2*^{-/-} HSPCs were transduced with lentiviral CRISPR and cDNA expression vectors and competitively transplanted into sublethally irradiated recipient mice (*n* = 5, per transduction condition) in order to engineer the following combinations of mutations: (1) *Tet2*^{-/-} + *Runx1*^{-/-} + *Ezh2*^{-/-}, (2) *Tet2*^{-/-} + *Runx1*^{-/-} + *Ezh2*^{-/-} + *Nras*^{G12D}, (3) *Tet2*^{-/-} + *Dnmt3a*^{-/-}, and (4) *Tet2*^{-/-} + *Dnmt3a*^{-/-} + *Npm1C* + *Flt3-ITD*. Peripheral blood samples collected at serial time points and harvested bone marrow will be analyzed by flow cytometry and histopathological methods to compare disease progression among mice. Following characterization of the generated models, they will be compared for their sensitivity to a standard chemotherapy regimen of doxorubicin and cytarabine.

By investigating the genetic basis for the heterogeneity in therapeutic responses observed in AML, the results of this study could be used to optimize the allocation of existing treatments to the most responsive patient subgroups. Furthermore, the models generated here could serve as reliable preclinical systems to test experimental therapeutic agents for AML developed in the future.

Detecting early articular cartilage degeneration via intra-articular fluorescence and radiographic imaging**Perry J. Hampilos****Harvard Medical School, William Bosworth Castle Society, Class of 2017****Thomas J. Gill IV, MD****Orthopaedic Surgery, Harvard Medical School**

Osteoarthritis (OA) is a common degenerative joint disease in which progressive loss of articular cartilage results in joint pain, reduced function and ultimately failure. Current disease models point to mechanical, biochemical and inflammatory pathways that mediate the breakdown of the articular surface and underlying tissue. Although the risk factors are well known, the early stages of joint degeneration need to be studied in order to diagnose OA earlier and more effectively mitigate further damage.

The main objective of this study was to develop a novel method to identify early stages of cartilage degeneration. We hypothesized that an imaging contrast dye could distinguish healthy cartilage from damaged areas. Rose Bengal is an iodinated fluorescent dye that binds collagen. We applied Rose Bengal to healthy and damaged (enzymatic and mechanical models) swine knee cartilage, and osteoarthritic human cartilage obtained from joint replacement surgeries. The stained cartilage was imaged via x-ray radiography and fluorescence/confocal microscopy, and analyzed for differential dye binding and tissue penetration.

Initial radiographic studies using concentrated radiopaque Rose Bengal in knee joints lacked adequate resolution, so we focused on the fluorescence approach. Fluorescence imaging of stained articular cartilage showed dye penetration into the lamina splendens and superficial region of healthy cartilage. Dye penetration was increased in mechanically and enzymatically induced tissue damage models. High resolution confocal microscopy revealed a pattern of reduced dye staining in enzymatically damaged tissue compared to healthy cartilage. In human OA cartilage, confocal imaging revealed tissue fibrillation, even in areas that did not appear grossly fibrillated.

The differential staining of Rose Bengal in healthy and damaged cartilage demonstrates the potential for in-vivo fluorescence cartilage imaging. Rose Bengal has been used safely in humans as an ophthalmic diagnostic agent and other medical applications. While more studies are needed to characterize its interactions with cartilage, this approach could be used to identify cartilage injury or surface micro damage, as well as enable further research on the early stages of joint degeneration. Better methods to diagnose early osteoarthritis will be instrumental in developing novel treatments to slow and reverse the progression of joint degeneration.

Targeting New Biomarkers of Thyroid Hormone Action**Meng Hao****Harvard Medical School, Francis Wendell Peabody Society, Class of 2017****Anthony Hollenberg, MD****Department of Endocrinology****Beth Israel Deaconess Medical Center**

Thyroid hormones (TH) are crucial regulators of human physiology including brain development, bone growth, nutrient metabolism, and body weight regulation. Currently, TH function in humans is determined by the serum thyroid stimulating hormone (TSH) level, which only reflects the effect of TH on the thyrotropin releasing hormone neurons in the hypothalamus and thyrotrophs in the anterior pituitary, and not the actions of TH on tissues such as the heart, liver, lungs, and bones. This study examined four potential new targets of thyroid hormone action from the methionine metabolic cycle including the enzymes methionine adenosyltransferase I (MAT1a), Betaine-homocysteine methyltransferase (BHMT), Adenosylhomocysteinase (AHCY), and Glycine N-methyltransferase (GNMT) as data from the laboratory has established that methionine cycle metabolites may be novel biomarkers of TH action. Levels of these four proteins were quantified through western blot analysis using liver extracts of PTU treated mice with subsequent treatment with either saline or T3 for 4 days. Protein quantification determined that the levels of AHCY ($p<0.01$) and GNMT ($p<0.05$) decreased in mice treated with T3, while the levels of MAT1a and BHMT did not show a significant change. This is congruent with studies measuring the mRNA levels in liver cells of PTU treated mice with saline and T3. The results of these studies show that AHCY and GNMT are likely regulated by thyroid hormone in order to control the production of circulating methionine metabolites. Future studies will aim to develop assays for examining changes in enzyme activity rather than the level of GNMT and AHCY to better understand the regulation of methionine metabolism by TH.

Investigating Circadian Rhythm in Acute Myeloid Leukemia**Matthew Heuton****Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017****George Q. Daley, MD PhD****HHMI****Boston Children's Hospital**

Acute myeloid leukemia (AML) is a heterogeneous malignant hematopoietic stem cell disease that results in overproduction of immature myeloid progenitor cells in the bone marrow. These cells compromise immune function and can lead to fatal infections. AML is responsible for approximately 35% of deaths from childhood leukemia.

Over 100 mutations have been implicated in the initiation and progression of AML, including genes involved in the control of circadian rhythm (CR). These CR genes are important regulators of hematopoiesis and preliminary data indicate their dysfunction may contribute to development and progression of AML. Altering expression of these genes may alter AML progression and lead to novel targets for therapy.

We hypothesized that downregulation of CR gene expression may alter the progression of AML. To test our hypothesis, we chose 15 CR genes to knockdown in cultured human bone marrow cells using shRNA. First, STBL3 cells were transformed with shRNA plasmid DNA. We used 4 different constructs for each of the 15 genes. The cells were then amplified in lysogeny broth (LB) and the DNA was purified using Qiagen Plasmid Maxi Kits. A restriction enzyme assay was performed to confirm the size of the plasmids we generated and 4 of the plasmids were sequenced to confirm the order of nucleotides. A virus to transduce K562 human bone marrow cells with the shRNA to be tested was created using Extreme Gene 9 transfection agent; a puromycin resistance gene was included in the plasmid. The K562 cells were characterized using established tissue culture techniques and a puromycin kill curve was established to select for cells that were successfully transduced with the shRNA plasmid.

Future work will determine whether or not the shRNAs that were generated are effective at knocking down gene expression in the K562 cells. shRNAs that are successful will be selected for knockdowns in human cord blood cells as well as mouse models of disease.

Identifying Early Changes in Myocardial Microstructure in Hypertensive Heart Disease**Pranoti G Hiremath****Harvard Medical School, Francis Weld Peabody Society, Class of 2015****Susan Cheng****Division of Cardiovascular Medicine
Brigham and Women's Hospital**

Hypertensive heart disease is characterized by a series of poorly understood pathophysiological changes within the myocardial tissue architecture, also known as the myocardial microstructure. Ultrasound imaging analysis can be utilized to assess incremental changes in the orientation and structure of myocardial fibers. A computational algorithm was used to investigate microstructure of the left ventricular myocardium through assessment of reflection intensity at the myocardial-pericardial interface. In B-mode echocardiographic images within humans with hypertensive heart disease as well as in a mouse model of afterload resistance, we analyzed the extent to which a novel algorithm can differentiate between normal myocardium and hypertensive heart disease.

We found that the algorithm significantly differentiated healthy controls (N=28) and individuals with uncomplicated essential hypertension (N=30, $P=0.025$). There was no difference between groups in total wall thickness ($P=0.37$) or left ventricular mass ($P=0.98$), although hypertensive individuals had a trend toward higher relative wall thickness compared to controls ($P=0.08$). In mice, animal groups that underwent sham procedure, temporary aortic banding, fixed aortic banding were more clearly differentiated by the algorithm ($P=0.026$) compared with left ventricular mass ($P=0.053$).

A novel imaging algorithm uses sonographic signal intensity analysis to provide an accessible non-invasive measure that appears to differentiate myocardium exposed to chronic afterload stress from normal ventricular microstructure. The algorithm may be especially sensitive to myocardial changes occurring early in the course of disease progression.

Cleft Severity by Sex in Non-Syndromic Cleft Lip and Palate Patients with the CLAP Classification Schema

Sara Hoge

Harvard School of Dental Medicine, Oliver Wendell Holmes Society, Class of 2017

Bonnie L Padwa DMD, MD

**Craniofacial Center, Department of Plastic and Oral Surgery,
Boston Children's Hospital**

Cleft lip and/or palate (CL/P) is the most common craniofacial birth defect worldwide. Cleft lip, with or without cleft palate, (CL±P) affects approximately 10.5/10,000 live births in the United States and isolated cleft palate (CP) accounts for approximately 6.4/10,000. Etiologic differences in these two phenomena are evidenced by the widely-reported gender disparity in the prevalence of each malformation. The incidence of CL±P in males known to be twice that of females, while the opposite is true for CP. The disparate sex distribution has been attributed to gender differences in the “threshold” for various teratogenic factors that may disrupt palatal closure; for instance, females demonstrate greater resistance to known cleft-inducing-factors in the maternal blood during embryonic development. While this may explain the lower incidence of CL±P in females, it remains unclear whether this genetic advantage is also a protective factor in terms of cleft severity or anatomical extent.

Based on the “threshold” model, we sought to identify if sex likewise confers a difference in severity or extent of the cleft noted in patients with CL±P. In previous studies, cleft severity has been more difficult to quantify due to limitations in the classification schema utilized to diagnose phenotypes in CL±P that do not describe the full range of morphological variants. In order to accurately evaluate cleft severity, we diagnosed and scored patients using the Cleft Lip and Palate (CLAP) classification system, a schema that can distinguish more subtle variations between phenotypic presentations of CL±P.

The medical records of 1068 patients with non-syndromic CL±P who had their primary repair at Boston Children's Hospital between 1980-2013 were reviewed. The sample included 681 males and 387 females, all of who were diagnosed and operated on by a single surgeon to ensure precision in diagnosis. The distribution and mean values for cleft type and severity score in males and females were compared using an independent samples t-test and non-parametric Wilcoxon signed rank test, and bivariate analysis was also performed with significance set at $p < 0.05$.

Our analysis found that there is no significant difference in cleft severity or distribution of cleft phenotype between male vs. female patients. These data indicate that although there may be a difference in “threshold” between the sexes in resistance to CL±P, manifesting in different incidences of the defect, the underlying mechanism determining the extent or severity of the cleft deformity is not affected by sex.

Scholarly Personal Narrative of Recovery after Trauma**Kaitlen S. Howell****Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017****John R. Peteet, MD****Department of Psychiatry****Brigham and Women's Hospital**

Scholarly personal narrative (SPN) is a method combining scholarly writing and personal narrative, which is used in many academic and professional fields. SPN acknowledges that personal experience contains valid information worthy of study and is one approach to the developing field of narrative medicine; it is especially powerful for giving voice to victimized populations and minorities. This project aims to create an SPN to depict the personal experience of a child and young adult seeking restoration of various aspects of life lost through extensive trauma. The first area of restoration examined is an objective measure: academic recovery and achievement after having only a first-grade education when beginning college due to forced non-attendance of school. The second area explored is the recovery of family after being taken away from biological parents as a young teenager, living in foster care, and being permanently estranged. The third is personal healing after extensive abuse and personal trauma.

The first step of writing an SPN is writing a memoir-style text of relevant experiences. To date, a memoir text covering fifteen years of trauma and the early years of the recovery process has been written. Many relevant themes have been identified (eg. spirituality and faith, resilience, forgiveness, etc.) and background research on these themes has been conducted, including primary literature, mainstream publications, and interviews with experts. The next steps are completion of the memoir text and identification of further themes. For my thesis, this manuscript will be transformed into an SPN via incorporation of the background research on all identified themes. The SPN will be written following the guidelines outlined in *Me-Search and Re-search: a Guide for Writing Scholarly Personal Narrative Manuscripts*.

The primary limitation expected in the approach to this project was that SPN is a relatively new and developing field. This has been addressed through reading SPN textbooks and examples and through consulting with narrative experts at Columbia University's Narrative Medicine program about this manuscript. The primary limitation of the finished project will be that this text describes the experience of only one person. Despite the focus on one person's experience, the scholarly themes will be generalizable to other trauma survivors' recovery. As few scholarly narratives exist on the subject of trauma and recovery, this project brings a unique new perspective to the fields of psychiatry, psychology, social work, social justice, and anyone helping trauma victims recover.

Psychosocial Needs of Young Breast Cancer Survivors in Mexico City, Mexico**Harper Hubbeling****Harvard Medical School, William Bosworth Castle Society, Class of 2017****Felicia Knaul, PhD****Harvard Global Equity Initiative, Department of Global Health and Social
Medicine****Brigham and Women's Hospital**

Breast cancer is the leading cause of cancer mortality in Mexican women and the second leading cause of overall death for young women (30-54). Mean age at diagnosis in Mexico is approximately a decade younger than in the U.S. and Europe.

Treatment practices generate specific challenges for young women. Due to late-stage presentation, mastectomy is more prevalent in Mexico than in the U.S., used in an estimated 85% compared to 37% of cases. While difficult for all women, younger women who might be considering childbearing, have young children, hold higher expectations for their appearance, be in less stable relationships, or at the peak of careers have particular issues coping with the complications of mastectomy and accompanying chemotherapy which include reduced arm strength/mobility, reduced reproductive lifespan, vaginal dryness, cognitive impairment, and a sense of mutilation.

Due to the recent implementation of national health care in Mexico, Seguro Popular, access to treatment is expanding, and with it the population of young survivors and need for a national survivorship care plan outlining long-term management of complications – psychosocial as much as clinical. Through our research we aimed to characterize the set of psychosocial issues unique to young survivors in order to inform the generation of a survivorship care plan addressing the needs of this population.

Twenty-five survivors (≥ 5 years since diagnosis) diagnosed prior to age 40 were interviewed at the Instituto Nacional de Cancerología (INCan) in Mexico City, the leading public cancer hospital serving primarily low-income women. Interviews were 30-60 minute one-on-one semi-structured conversations in Spanish, following a topic guide exploring psychological aspects (current state/life perspective/self-confidence), social aspects (family/friends/partners/children), employment/activities, religion/spirituality, body image and fertility. Interviews were recorded, transcribed and coded in Spanish using NVivo. Findings are limited to the experience of INCan patients.

Initial analysis revealed several actionable unmet needs. Patients wanted more integrated psychological care continuing beyond treatment. Many desired information about diet, lifestyle and primary care. Almost all stopped working during treatment and many experienced hiring discrimination. Body image distress varied across time and was linked to partner rejection, stigma, and self-confidence loss. Women did not discuss fertility with physicians, and, contrary to existing international literature, patients were not concerned about fertility at diagnosis regardless of prior desire to conceive.

These results highlight the need for survivorship planning conscious of the distinct psychosocial needs of young breast cancer survivors, particularly regarding fertility, information, financial protection, and medical and social service interventions.

Stories Speak – Using Patient Stories to Engage Patients and Co-Design Care among Patients Classified as “High Utilizers” at Cambridge Hospital

Carly Elizabeth Hudelson, MSc
Harvard Medical School, Francis Weld Peabody Society, Class of 2017

Yamini Saravanan, MD
The Primary Care Center, Cambridge Hospital
Cambridge Health Alliance

National health reform efforts are increasingly focused on a small group of patients classified as “high utilizers” who account for disproportionately high rates of spending and are often frequent utilizers of the Emergency Department (ED). Complex care management (CCM) teams have been formed to coordinate care to better meet the needs of this population, but they have not been uniformly successful. The patient’s voice has largely been absent from these efforts, and there is a paucity of literature focused on better understanding the perspective of patients characterized as “complex”. Who are these patients, and what is the patients’ assessment of her/his own health needs? Engaging these patients to co-design their care is essential for improving care and reducing unnecessary utilization among this population.

This project aimed to elicit the stories of high-utilizing patients at Cambridge Health Alliance (CHA) in order to understand their experiences and needs in their own voice. We contacted and elicited the stories of patients who were classified as high-utilizers within CHA, were covered by Medicaid, and had more than six ED visits within the past year. We used a combination of narrative inquiry and semi-structured interview methods in order to capture the patients’ personal story, health experiences, and needs and goals for their own health. We used thematic analysis to systematically extract themes. We also created a one page story for each patient, which was returned to the patient and incorporated into her/his electronic medical record.

We were able to engage twelve patients to share their stories. All patients were struggling with psychiatric comorbidities and many were homeless with unaddressed social needs contributing to their ED utilization. Several other important themes emerged from our analysis, including the need for better communication and home visits. These were not captured in the patients EMR.

The people behind the label of “complex” and “super utilizers” constitute a heterogeneous group for which there is no one-size-fits-all solution for improving care. Better addressing the needs of this group with necessarily involve understanding the complex forces driving ER admissions so that they can be advocated for and better connected with various services they need in order to be healthy. This project demonstrates a process by which a story-based approach can provide much-needed context and nuance to existing information in patients’ electronic medical record and can be used as a tool to engage patients and strengthen relationships between patients and care teams.

Race and ethnicity as predictors of pregnancy and live birth after in vitro fertilization: a systematic review

Leigh Ann Humphries

Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Michele R. Hacker, ScD, MSPH

Department of Obstetrics and Gynecology

Beth Israel Deaconess Medical Center

Although women undergoing in vitro fertilization (IVF) in the United States remain predominately Caucasian, increasing racial and ethnic diversity of patients accessing IVF in the U.S. and internationally has led to insights about the impact of race and ethnicity on pregnancy and live birth rates. Numerous studies have reported racial and ethnic disparities in IVF outcomes, particularly in black, Asian, and Hispanic women relative to Caucasian women, independent of other factors. This systematic review analyzes comparisons of IVF outcomes (pregnancy and/or live birth rates) based on race and/or ethnicity. By summarizing published data for each race/ethnicity, rather than for each outcome, this review may help patients and clinicians better assess the success rates for an individual patient seeking infertility treatment.

We searched PubMed, EMBASE, Web of Science, CINAHL, POPLINE, and Cochrane Central databases in July 2013 for studies that reported IVF outcomes as well as race and/or ethnicity designations, including but not limited to black, white, non-white, Caucasian, Asian, Hispanic, and Latino/a. Following the PRISMA guidelines, two independent reviewers evaluated 1,525 abstracts and selected studies that reported original data on pregnancy and/or live birth rates after non-donor IVF cycles in populations stratified by race/ethnicity.

Of 1,525 studies citations reviewed, 22 full-text studies met the inclusion criteria. Black, Asian, and Hispanic populations have lower pregnancy and/or live birth rates after fresh, non-donor IVF cycles than white or Caucasian women according to all five U.S. registry-based studies and the majority of smaller observational studies. Notable variations in methodology, including definitions of race/ethnicity and covariates used in the models, likely influenced study findings. Potential explanations for these outcome disparities include racial/ethnic differences in access to care, etiology of infertility, comorbidities, genetic polymorphisms, ovarian function, and hormone levels. It is unclear to what extent these and other potential confounders may drive racial and ethnic disparities in outcomes. In addition, some studies that evaluate the influence of race/ethnicity are limited in their ability to draw conclusions given the substantial proportion of missing race/ethnicity data.

Existing evidence points to race and ethnicity as strong predictors of IVF outcomes; however, more research is necessary to determine the influence of potential confounders in these populations. Race/ethnicity likely is a surrogate for many tangible and intangible factors that lead to differences in outcomes, including biological, environmental, social, and cultural factors that are often difficult to measure and may not be captured in a clinical setting. This review highlights the need for studies that systematically investigate etiologies of such disparities and in turn inform practices that minimize inequalities.

Development and Validation of a Survey on School-Based Oral Health Programs in Massachusetts**Alexander A.J. Jelicich****Harvard School of Dental Medicine, Walter Bradford Cannon Society, Class of 2017****Christine Riedy, PhD, MPH****Department of Oral Health Policy and Epidemiology
Harvard School of Dental Medicine**

School-based oral health programs take place at many schools throughout the nation in order to promote proper oral health and hygiene practices and screen children for dental disease. In February 2014, DentaQuest Foundation released goals for their “Oral Health For All 2020” initiative which included having, “oral health incorporated into [the] primary educational system.” The measurable objective was that the 10 largest school districts will have incorporated oral health into their systems within the next six years. Although statewide oral health screenings have been conducted in Massachusetts (MA) schools to determine the rate of children’s dental disease, to our knowledge, there have not been studies on the school-based oral health education programs and services currently being delivered. Therefore, an important first step is to develop a comprehensive survey to identify and describe the current school-based oral health programs. The current study aimed to develop and validate a survey to better understand the school-based oral health programs currently being delivered in MA schools.

Prior to development of the survey, five key informant interviews were conducted to understand the best implementation procedures for the survey. Interviews were audio recorded and analyzed for thematic content. Interviews revealed that school nurses are the most appropriate person to survey regarding their schools’ oral health education programs. Additionally, respondents indicated that the best time to pretest the survey was in late fall, after schools have resumed and administrative tasks related to back-to-school activities have been completed.

Survey development consisted of several steps including framing topics, writing and ordering questions/items under the topics, and creating a common visual stimulus using the SurveyMonkey.com platform. Pretesting of the survey to ensure validity and reliability will occur in late fall of 2014 and will include evaluation from experts using the Question Appraisal System, cognitive interviews (N=10-15) and collection of survey data from a subsample (N=50) of school nurses within the greater Boston area. Pretesting will provide additional feedback before the survey is finalized for wider distribution. The present project will not include the actual execution of the final survey. After the above steps have been completed, the final survey will be administered to all MA primary schools. Results from the final survey will allow for analysis of the differences in MA school-based oral health education programs and services.

**Measuring Baseline HIV and Hepatitis C Screening Efficacy in an MGH
Community Health Center**

Nicholas J. Jensen

**Harvard Medical School, Walter Bradford Cannon Society, Class of 2017
Foster Scholars Program**

**Marya J. Cohen, MD, MPH
Department of General Medicine
Massachusetts General Hospital**

The Crimson Care Collaborative (CCC) student-faculty clinic at MGH Chelsea provides primary care services to many patients who have historically had difficulties accessing routine primary care, including detection of chronic—but treatable—diseases like HIV and hepatitis C virus (HCV). Successfully treating these chronic diseases depends upon early diagnosis of infection, but the CCC Chelsea has not yet evaluated how well its patients are being screened for HIV and HCV. Additionally, with the development of a free tattoo removal clinic at MGH Chelsea, the CCC is investigating the prevalence of tattoos among its patients' and their interest in tattoo removal services.

Our first objective was to determine HIV and HCV screening rates among CCC Chelsea patients. We conducted a chart review of patients enrolled in the study to calculate the percentage of patients who were screened for HIV and hepatitis C in accordance with U.S. Preventive Services Task Force (USPSTF) guidelines. Patients whose records demonstrated that they were screened for HIV and HCV (if indicated) prior to or within one month of their initial CCC Chelsea visit were considered appropriately screened.

Our second objective was to determine the prevalence of tattoos among CCC Chelsea patients and to gauge tattooed patients' interest in free tattoo removal services. We administered a questionnaire to participants during the clinic to identify patients with tattoos and to assess their interest in tattoo removal. This questionnaire was also used to identify risk factors in each participant that indicated HIV and HCV screening.

Currently, 48 patients are enrolled (28 males, 20 females), with an average age of 40 years. Of patients indicated for HIV screening, 23% were screened before their initial CCC visit, 58% within 1 month of their first visit, 14% more than 1 month after their first visit, and 5% have not been screened. Of patients indicated for HCV screening, 25% were screened before their initial CCC visit, 44% within 1 month of their first visit, 25% more than 1 month after their first visit, and 6% have not been screened. 15% of participants are tattooed, and of these, 71% are interested in free tattoo removal services.

This ongoing project is helping to ascertain CCC Chelsea's rates of HIV and HCV screening and adherence to USPSTF guidelines—data which will inform future quality improvement projects. Additionally, the study's questionnaire is the first step in designing and establishing the free tattoo removal clinic at MGH Chelsea.

**Palliative head and neck radiotherapy with the QUAD SHOT regimen
for incurable primary or metastatic cancers**

Ginger Y. Jiang

Harvard Medical School, Frances Weld Peabody Society, Class of 2017

Benjamin Lok, MD and Nancy Y. Lee, MD

**Department of Radiation Oncology
Memorial Sloan Kettering Cancer Center**

There is significant literature describing the definitive treatment of head and neck cancers using radiation therapy (RT); less understood is palliative RT treatment in patients with incurable head and neck cancers. Patients with advanced local disease, metastatic disease, or co-morbidities may not be candidates for aggressive RT with curative intent, but may still benefit from a palliative RT regimen. Given the importance of head and neck structures to daily function, local progression of head and neck cancer can cause significant morbidity and psychological distress. Palliative RT can help achieve local control and symptomatic relief.

A cyclical hypofractionated palliative radiotherapy regimen (QUAD SHOT) was developed to maximize palliation while minimizing toxicities. The QUAD SHOT regimen comprises 370 cGy fractions given twice a day over 2 days at 2-3 week intervals up to a total dose of 4400cGy. We report on the institutional experience of MSKCC with the QUAD SHOT regime in head and neck cancer patients.

Our study included seventy-five patients who completed at least 1 cycle of palliative RT to the head and neck at MSKCC between February 2005 and July 2014. Palliation was defined as relief of presenting symptom(s) or tumor response, determined clinically or radiographically. Toxicity was scored using the NCI CTCAE v3.0. Overall survival (OS) was estimated by the Kaplan-Meier method. The Spearman's rho test was used to determine correlation between palliative response and clinical factors.

The median patient age was 72 years; 57% were male. The most common histologies were squamous cell carcinoma (51%), thyroid carcinoma (17%), and salivary gland carcinoma (13%). Recurrent or primary T-stages were: T1 (3%), T2 (16%), T3 (20%), T4 (47%), T0/Tx (12%). Forty-nine percent of patients had prior surgical resection at the primary disease site; 40% received prior RT at the palliative site. Most common presenting symptoms were pain (51%) and dysphagia (23%). Sixty-five percent of patients had a palliative response. Median overall survival was 5.67 months (range, 0.2 - 34.5). The rates of grade 3 and grade 2 toxicity were 7% and 28% respectively. Palliative response was significantly correlated with increasing number of QUAD SHOT cycles ($p = 0.027$) and increasing KPS ($p = 0.004$), but not prior RT, prior surgery, histology or T-stage. Palliative response carried a reduced risk of death ($HR = 0.23$).

In conclusion, we found that the QUAD SHOT regimen produced excellent rates of palliative response with minimal toxicity. Completion of a greater number of QUAD SHOT cycles was correlated with enhanced palliative response and survival.

Refer Smarter: Connecting Codman Square Health Center PCPs with Specialty Knowledge

Stacy Jones

Harvard Medical School, Walter Bradford Cannon Society, Class of 2017

**Ian Huntington MD, MPH
Internal Medicine Department
Codman Square Health Center**

Codman Square Health Center is a community-based, multi-service outpatient center located in Dorchester, Massachusetts. Codman serves a diverse population of about 20,000 patients, and provides mostly primary care services within its medical practice. Many of these primary care visits result in referring a patient to a specialist; about 600 specialty referrals per month are submitted from Codman to its primary hospital affiliate, Boston Medical Center. Unfortunately, the supply of specialty appointments does not adequately meet the demand of referred patients – about 70-100 unscheduled referrals are in queue at any point in time, and patients may wait over two months for their appointment to be scheduled.

Our objective is to improve the specialty referral process at the health center by providing an online system in which primary care providers (PCPs) at Codman can quickly and efficiently receive specialty opinions. The platform, RubiconMD, allows a PCP to upload a patient case and a question for a specialist. All patient information is de-identified and sent asynchronously to one of RubiconMD's specialists, who respond to the case within hours.

We hypothesized that such a system would improve the quality and efficiency of care by enhancing the PCPs' knowledge base, decreasing avoidable specialty referrals, and optimizing necessary referrals by ensuring they are sent with appropriate laboratory and imaging results. Furthermore, we predicted that both empowering PCPs to treat patients within their primary care clinics and decreasing the flux of patients referred to a specialist would minimize the time between initial presentation and treatment.

As of October 2014, 5 of the 22 Codman PCPs have utilized the platform, and a total of 13 cases have been submitted to 7 different specialties. Five cases were submitted to endocrinology, two cases were submitted to urology, and one case each was submitted to dermatology, nephrology, pulmonology, hematology/oncology, orthopedic surgery and gastroenterology. The average response time was 8.98 hours. Market research done by RubiconMD surveyed 4 of the 5 active users, and results indicated that 3 out of 4 respondents feel the RubiconMD platform moderately enhanced their ability to care for patients. Additionally, on average the respondents agreed that using RubiconMD empowers them to take care of similar patients.

Maintaining physician engagement and recruiting non-users remains a challenge. This project is ongoing, and future plans include conducting qualitative interviews with Codman PCPs and administrators in order to assess platform impact, areas for improvement, and to address long-term sustainability.

Immigrants' Knowledge of Insurance and its Affordability under Massachusetts Health Reform**Ye jin Kang****Harvard Medical School, William Bosworth Castle Society, Class of 2017****Leah Zallman, MD MPH****Division of Social and Community Medicine, Department of Medicine
Cambridge Health Alliance**

Background: Despite insurance expansion under the Affordable Care Act (ACA), concern remains that access to insurance for immigrants will be limited. Immigrants will gain insurance through Medicaid expansion and subsidized private insurance. However, undocumented and legally present immigrants in the US for <5 years will be barred from federally sponsored coverage. The Massachusetts (MA) 2006 health reform, on which the ACA was modeled, contained some features that allowed insurance access for immigrants. However, no studies have investigated immigrants' experience with affordability of care and knowledge of insurance under MA health reform.

Methods: Between August 2013 and January 2014, we conducted face-to-face surveys of a convenience sample of 1306 (response rate of 81%) patients in three Emergency Departments of the 2nd largest safety net institution in MA. We assessed knowledge about insurance and views on affordability of care and insurance. We first determined the percentage of immigrants and non-immigrants experiencing each outcome, and then performed comparisons using chi square analyses. Finally, we conducted age and gender adjusted logistic regression analyses.

Results: Immigrants reported higher levels of financial burden (17% vs 12%, $p=0.0163$), reported more difficulty affording their insurance (14% vs 9%, $p=0.0141$) and were more concerned about paying their premiums (28% vs 11%, $p=0.0003$). Immigrants were less likely to know their copayment for regular doctor visits and medications (44% vs 58% , $p=0.0002$), less likely to have insurance information in their primary language (29% vs 1%, $p<0.0001$), and more likely to report that signing up for insurance would be easier with fewer plans (50% vs 33%, $p=0.0187$). Among those with any chronic disease, immigrants reported no more cost-related barriers to seeking medical care (28% vs 30%, $p=0.6294$). Overall, adjustment for age and gender did not alter the findings.

Limitations: This was a convenience sample of patients presenting for emergency care at one safety net institution; results may not be generalizable to other populations. In addition, patients were already accessing care, which may have selected for patients who had knowledge and could afford care.

Conclusions: These results suggest that despite additional efforts to provide affordable insurance and information for all residents under MA health reform, immigrants continued to experience lower affordability and knowledge of insurance as compared to non-immigrants. Because access to insurance will be more restricted under national implementation of the ACA, our findings suggest that disparities in affordability and knowledge about insurance for immigrants may persist under the ACA.

Lessons in global palliative care education from developing and implementing a curriculum in Belarus

Alexander Kazberouk
Harvard Medical School, Castle Society, Class of 2017

Sarah Slater, MD
Dept. of Hematology, Oncology, and Palliative Medicine, Mount Auburn Hospital

The WHO and the Worldwide Palliative Care Alliance recently mapped supply and demand for palliative care worldwide, finding that only 10% of the 20.4 million people who need palliative care currently receive it. A major barrier to meeting that need is insufficient education of healthcare workers. Access to opioids and other essential drugs is another fundamental component of palliative care, but the policy shift to allow access has been slow in many countries.

We report on the experience of developing and implementing a palliative care curriculum in Belarus, a country where palliative care is a relatively recent development. In the past ten years, the field of palliative care has attracted significant interest from the government of Belarus and non-government agencies, with the first adult hospice founded in 2005 and palliative care introduced into the National Healthcare Law in 2014. However, the country faces a shortage of healthcare providers trained in palliative care and additional challenges, including barriers to opioid availability.

To develop the curriculum, we conducted a needs assessment that examined physician attitudes towards end of life care, the legal status of palliative care, drug availability, and other topics. We utilized past in-country experience, a literature review, a questionnaire, and interviews with our Belarusian colleagues. Based on the needs assessment, we developed, modified, and translated a 25-lecture curriculum that was comprehensive, at the proper difficulty level, and culturally appropriate. A team of four clinicians and a medical student taught the curriculum in Belarus over five days to an audience of oncologists, general practitioners, palliative care physicians, and healthcare administrators. To evaluate the course and adjust our teaching, we developed daily and end-of-course surveys utilizing Likert scale satisfaction, relevance questions and qualitative responses visualized using the Tag Cloud methodology. The course was well-received - participants were satisfied, reported a better understanding of palliative care and improved their skills in managing symptoms and discussing prognosis.

We hope to continue collaboration with Belarusian colleagues, especially in light of new government policies promoting palliative care and a recent initiative to develop a National Palliative Care Center. The materials we developed - a needs assessment, a palliative care curriculum, surveys, and a set of success factors for a palliative care course - may also be used for education beyond Belarus. Ultimately, we hope that our experiences and materials provide encouragement and resources for additional palliative care education and development worldwide.

Improving Value in Spine Care by Understanding Drivers of Cost Variation in Spine Surgery and Examining Innovative Reimbursement Models

Alexander Kazberouk

Harvard Medical School, William Bosworth Castle Society, Class of 2017

Kevin J McGuire, MD, MS

Department of Orthopaedics, Beth Israel Deaconess Medical Center

Annually, \$90 billion is spent in the United States on medical expenses for low back pain; losses in productivity account for an additional \$10 to \$20 billion. While some of the spending is warranted, tremendous resources are being spent on costly, guideline-discordant care that is not cost-effective. Two factors driving wasteful spending are unwarranted variation in the provision of necessary services and the provision of unnecessary services due to the incentives from the existing volume-oriented fee-for-service system.

To address the issue of unwarranted inter-provider variability, we examined 1,407 cases of spine surgery at a single institution over three years broken down into 5 procedure types accounting for over \$23M in total hospital spend. We identified variation in median cost between highest and lowest cost physician with substantive case volume ranging from 1.33 to 1.75-fold depending on the procedure with posterior lumbar decompression being the most variable and posterior laminectomy the least. In general, supply cost was the primary driver of variation followed by operating room and anesthesia costs. Spending on labs, radiology, ICU, pharmacy, and other areas contributed less to variation in total cost. We are conducting additional analyses to case-adjust and validate the significance of the variation as well as to calculate the opportunity of reducing variation.

To examine how institutions are shifting away from volume-driven reimbursement incentives, we surveyed 20 stakeholders at 16 institutions setting up or helping to set up innovative reimbursement models for spine surgery. Most models examined were variations of bundled payments wherein a flat fee covers preadmission work, the hospital stay, and post-acute care with the physician held responsible for cost and appropriate utilization. Through semi-structured interviews, we developed case studies and a framework for examining highly heterogeneous bundled payment programs for spine procedures. The framework addressed the payor or purchaser, provider specialties involved, conditions covered, procedures included, and payout mechanics. We also identified success factors consistent across institutions, including approaches to limiting risk, the importance of including physicians, and the need to develop care pathways prior to financial model roll-out. Finally, we saw that while bundled payments for acute services are a first step, policymakers and healthcare providers are also beginning to consider global-risk payment models that focus on both surgical and non-interventional spine care. We hope to share the experiences of early adopters to encourage other providers to shift to risk-based reimbursement models such as bundled payment and global payment models.

A Retrospective Chart Review of Pediatric Nonmelanoma Skin Cancer**Hasan Khosravi****Harvard Medical School, Walter Bradford Cannon Society, Class of 2017****Jennifer Huang, MD****Department of Dermatology, Boston Children's Hospital**

Nonmelanoma skin cancer (NMSC) in children is rare and thus, often overlooked or misdiagnosed. Most cases have been reported as individual cases or small case series in association with certain predisposing acquired and hereditary conditions. The primary aim of this study was to explore the characteristics of pediatric NMSC at Boston Children's Hospital (BCH) over a 21 year time span.

A retrospective chart review was performed on all patients at BCH under age 30 with a histopathologic diagnosis of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) between 1993 and 2014. Demographic, clinical, histopathologic, and radiologic data were extracted from medical records and characterized using descriptive statistics.

A total of 7 patients with SCC, 20 patients with BCC, and 2 patients with both BCC and SCC were identified. 4 patients had more than one SCC, and 7 patients had more than one BCC. 83.3% of all patients were of white race, and 80% were of Fitzpatrick skin phototype I or II. Predisposing conditions in patients with SCC included prior site of chronic inflammation (3), prior site of wart (2), history of chemotherapy or radiation (5), and history of immunosuppression (6). Predisposing conditions in patients with BCC included nevus sebaceous (6), Gorlin syndrome (6), history of immunosuppression (8), and history of radiation (14). Of the two patients with both BCC and SCC, one was diagnosed with xeroderma pigmentosa while the other underwent bone marrow and double lung transplant. One SCC and one BCC patient had no identifiable risk factors. The majority of all patients were treated with surgical excision. The mean # days from time of lesion onset to diagnosis was 667 for SCC and 1074 for BCC. Mean # of visits prior to diagnosis was 1.3 for SCC and 1.4 for BCC.

NMSC in children is rare, with only 29 cases of NMSC identified at a tertiary academic pediatric hospital over a 21 year period. The vast majority of patients were Caucasian and had additional identifiable risk factors. The majority of patients had multiple NMSC, suggesting that patients with an initial NMSC diagnosis should be closely monitored. There was a significant delay in diagnosis in the majority of cases, but few visits required, suggesting that patients and their parents may not be aware of the signs of NMSC. Patient education regarding NMSC surveillance should be considered in high risk groups.

Antibiotic Resistance in Severe Orofacial Infections**Min Kyoung Kim****Harvard School of Dental Medicine, Francis Weld Peabody Society, Class of 2017****Meredith August, DMD, MD****Department of Oral Maxillofacial Surgery****Massachusetts General Hospital**

Treatment of severe infection requires adequate surgical drainage of the sites involved followed by appropriate use of antimicrobials. Despite seemingly appropriate therapy, serious complications including mediastinitis, thoracic empyema, pericarditis, septic shock, and intracranial spread of infection can occur. Traditionally, high dose penicillin or clindamycin were reasonable empiric first line antibiotic choices. However, penicillin and clindamycin resistance in microbial isolates from head and neck infections have been reported. In this review, we studied if there are emerging patterns of antibiotic resistance in orofacial infections compared to the historic cohort treated a decade earlier. We also studied how often empiric antibiotic therapy needed to be altered based on culture and resistance data in the current patient population. Lastly, we studied whether the presence of resistant bacteria led to a prolongation of hospital course or more complicated in-hospital treatment and increased overall cost of in-hospital treatment.

We identified 61 cases of head and neck infections requiring hospital admission, surgical drainage and IV antibiotics treated from 2009-2014 at Massachusetts General Hospital; there were 37 males and 24 females, with average age of 45 years and length of stay averaging to 5.5 days. We evaluated the microbiology of these infections, including resistant isolates. Out of the 81 isolated cultures, 31% of penicillin resistance and 30% of clindamycin resistance were found. The antibiotics given in the hospital were changed 12 of the cases. The antibiotic resistance data will be compared to historic data in a tertiary care setting but treated a decade earlier (1997 to 2003 at urban tertiary care center in NJ) to study if the resistance is on the rise. Additionally, the clinical course of these patients was noted. Overall cost of in-hospital treatment will be calculated from this data.

To see if there was a correlation between antibiotic resistance and other variables, logistic regression analysis will be done. Clinical variables that reflect the severity of infection as well as other variables of past medical history will be noted in the univariate logistic regression analysis. These clinical variables significant in the univariate analysis will be further analyzed in the multivariable logistic regression analysis. Potential correlation between antibiotic resistance and length of stay or cost of in-hospital treatment will be assessed through linear regression analysis.

A limitation of this study is that there may, despite our best efforts, be differences in the two cohorts in terms of demographics, medical history, and other regional variations.

Daytime Wetting in Elementary Schools - Results from a cross sectional teacher survey

Lauren N. Ko

Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Hillary L. Copp, MD, MS

Department of Urology

University of California – San Francisco

Students spend a significant portion of their waking hours in the classroom. Dysfunctional voiding in school-aged children is a well-known problem, comprising of almost half of all pediatric urology referrals, yet data on teacher practice regarding bathroom use and daytime accidents, as well as the extent of educator training on the topic is lacking. This cross sectional survey study sought to better characterize the experience of teachers who witness dysfunctional voiding in the school setting, and the role teachers may play in mitigating unhealthy learned bathroom behaviors. These deleterious behaviors can contribute to bladder and bowel dysfunction, thus rendering regular bladder emptying critical in both the prevention of infection and maintenance of urinary tract health.

After recruitment via social media, elementary school teachers, age 20-60 years old, completed an online survey regarding their teaching experience, their policies on student bathroom use, student access to water, the state of the school bathrooms, and their course of action in cases of accidents. Further, teachers were inquired about whether they received professional development on this health issue. The primary outcome was to determine the factors leading to promotion of unhealthy voiding patterns, which were defined based on answers to several survey questions. Factors associated with unhealthy voiding patterns were identified using multivariate logistic regression.

Of the 4166 teachers that completed the survey, 87.9% of teachers indicated that they encourage students to hold their urine. 36% teachers have a protocol in place to encourage holding, and 67.5% of these protocols are rewards-and/or consequence-based. Despite these strict bathroom protocols, 80.5% of teachers allowed their children unlimited access to water. 84.9% of teachers indicated that serious behavioral issues occur in their school bathroom. 81.7% of teachers reported never having any professional development on this health issue. Overall, 76.2% teachers promote unhealthy voiding behavior, most commonly associated with larger teacher to student ratio, upper elementary grades, and lack of previous training on the subject.

Students spend substantial time in school and educators can play a key role in maintaining the health of a child's urinary tract. Currently, teachers lack training on the urological issue, which may contribute to the promotion of unhealthy voiding behaviors, especially with consideration of upper elementary teachers and classrooms with fewer teachers. This study suggests that pediatricians and urologists who suspect children have or are at risk of developing BBD should communicate with both parents and teachers to discourage harmful voiding patterns.

Impacts of allocation of insulin and diabetes supplies on diagnosis, treatment and self-management of Type 1 diabetic patients at the Central Hospital of Yaoundé

Nelly-Ange T. Kontchou

Harvard Medical School, Walter Bradford Cannon Society, Class of 2017

Dennis Ross-Degnan, PhD

Department of Population Medicine

Harvard Pilgrim Healthcare Institute

With its health system now confronting a shared burden of infectious and noncommunicable diseases, the sub-Saharan nation of Cameroon must weather this epidemiological transition. Specifically, diabetes mellitus affects 3.5% of the population and 6-7% of adults in urban milieu. Type 1 diabetes represents 10% of total prevalence and contributed to the more than 200% increase in diabetes-related mortality between 2004 and 2011. Management of Type 1 diabetes is particularly challenging in resource-poor settings because patients depend on a steady, reliable and affordable supply of insulin to stay alive.

Access to insulin and supplies to monitor blood glucose is central in Type 1 diabetes. This study aimed to characterize the supply chain for insulin and materials like syringes and glucose meters to the Central Hospital of Yaoundé, assess health professionals' ability to diagnose and treat Type 1 diabetes with their available resources, and examine how affordability and accessibility of treatment materials affect patients' modes of self-management.

To achieve these aims, semi-structured interviews were administered to 10 patients, 6 health professionals, 2 pharmacists, 1 laboratory assistant and 4 key informants: the sub-Director of the Ministry of Public Health's Department of Pharmacies, Drugs and Laboratories, a representative from insulin manufacturer Novo Nordisk, the Director of Procurement at CENAME central drug store and the founder of *La Maison des Diabétiques*. All interviews were transcribed, and quantitative data was summarized using descriptive statistics.

Key informants explained that the Minister of Public Health authorizes CENAME to import only human insulin from Novo Nordisk at the 78.6%-subsidized rate of \$6.00 per 10mL because analog insulin is too costly. Determination of annual requirements of insulin, syringes and needles, glucose meters, test strips and lancets, however, is hampered by sub-optimal recordkeeping. So, when the hospital's stock runs out, patients must purchase from expensive private pharmacies. Seven patients (70%) had experienced financial shortage from treatment costs, but only four (40%) stopped treatment in response. The laboratory assistant revealed no technical difficulties in testing and diagnosing patients, and 5 health professionals (83.3%) listed patients' lack of money as the largest obstacle to their work.

These data suggest that though the Cameroonian government has mitigated the price of insulin for patients, patients still struggle with insulin administration without access to flexible analog protocols. Moreover, patients' financial limitations, more than hospital resources, limit physicians in diagnosis and treatment. Finally, the majority of patients compromise their self-management due to financial constraints.

Comparing the efficacy of antibiotics versus oral contraceptives in Acne Vulgaris**Eubee B. Koo****Harvard Medical School, Francis Weld Peabody Society, Class of 2015****Tyler D. Petersen****Western University of Health Sciences, College of Osteopathic Medicine of the Pacific****Alexandra B. Kimball, MD, MPH****Clinical Unit for Research Trials in Skin, Department of Dermatology
Massachusetts General Hospital**

Acne vulgaris is a common inflammatory disease of the pilosebaceous unit, affecting approximately 40 to 50 million people in the United States alone. It is characterized by a variety of lesions ranging in severity from open and closed comedones of the face in mild cases to pustules, papules, nodules, and cysts of both face and trunk in severe disease. Various medications have been found to be effective in the treatment of acne, including oral antibiotics and oral contraceptive pills; to date, however, despite widespread use of both medications, few direct comparisons of efficacy between the two modalities have been published. The purpose of the study was to determine which is more effective in the treatment of acne vulgaris.

To address this question, a meta-analysis was conducted in accordance with PRISMA and Cochrane collaboration guidelines. A review of 226 publications yielded 32 randomized control trials that met our inclusion criteria.

We found that at 3 and 6 months, compared to placebo, both antibiotics and OCPs effected greater percent reduction in inflammatory, non-inflammatory, and total lesions; the two modalities at each time point demonstrated statistical parity, except that antibiotics were superior to OCPs in percent reduction of total lesions at 3 months (weighted mean inflammatory lesion reduction: Abx3=53.2%, OCP3=35.6%, Plac3=26.4%, Abx6=57.9%, OCP6=61.9%, Plac6=34.2%; weighted mean non-inflammatory lesion reduction: Abx3=41.9%, OCP3=32.6%, Plac3=17.1%, Abx6=56.4%, OCP6=49.1%, Plac6=23.4%; weighted mean total lesion reduction: Abx3=48.0%, OCP3=37.3%, Plac3=24.5%, Abx6=52.8%, OCP6=55.0%, Plac6=28.6%).

From this data, we ascertained that 1) both antibiotics and OCPs used as monotherapy are effective in the treatment of acne vulgaris, and 2) while antibiotics appeared to have a therapeutic advantage over OCPs at 3 months, by 6 months, OCPs rivaled antibiotics in producing similar percentage reductions in lesions. Thus, for select women with acne, OCPs may be a more appropriate first-line long-term preventive modality for acne, as antibiotics are associated with various side effects including the underdiagnosed induction of *Malassezia* folliculitis and the much less common development of bacterial resistance with prolonged use.

Cranial Nerve Injury after Temporomandibular Joint Surgery**Sungeun Stephanie Koo****Harvard School of Dental Medicine, William Bosworth Castle Society, Class of 2017
Department of OMFS Education and Research Fund****David A. Keith, DMD, BDS****Department of Oral and Maxillofacial Surgery
Massachusetts General Hospital**

Cranial nerve VII or facial nerve is a very complex nerve with many functions: motor, sensory and parasympathetic innervation. In a recent study by Hohman et al. reviewing the epidemiology of facial nerve injuries during surgery, it was found that oral and maxillofacial surgical (OMFS) procedures accounted for 40% of injuries. Among many OMFS procedures, temporomandibular joint (TMJ) surgery was found to be the most common operation resulting in facial nerve injury. In this study, we aim to focus on the patients who developed iatrogenic facial nerve injury during TMJ procedures to determine the etiology, recognize the risk factors and make recommendations to reduce the incidence.

Out of 1,810 patient records from the Seventh Nerve Clinic at Massachusetts Eye and Ear Infirmary (MEEI) that were reviewed in the study conducted by Hohman et al., 102 were referred for iatrogenic facial nerve injury after resections of head and neck lesions and other surgical interventions. 28 patient cases were related to TMJ replacement operations, comprising 68% of injuries from oral surgical procedures. Records will be reviewed for age, gender, types of surgery, surgical technique, prior surgical interventions and outcome in terms of CN VII function. Age, gender, side, diagnosis, prior procedures, type of surgery performed will be recorded. Within the operation notes, difficulties encountered, types of nerve monitoring, details of dissection, surgical time, and blood loss will be documented. After quantifying the patient data and summarizing the descriptive features on the operation reports, the data will be compared to the information from the patient sample of the prior study done by Hohman et al.

The data have been organized in a table and the statistical analysis will be conducted soon.

**Developing a mobile health application for community health screening
in Chiayi, Taiwan**

Christine Er-zhen Kuo
Harvard Medical School, Francis Weld Peabody Society, Class of 2017

Li-Li Hsiao, MD, PhD
Asian Renal Clinic, Department of Nephrology
Brigham and Women's Hospital

Mobile health technology has become an increasingly popular means for providing accessible health care and services to otherwise underserved peoples. Smartphone applications (apps) in particular have been highly utilized by community health workers to deliver effective primary care out in the field. Incorporating the use of mobile apps within the hospital system provides a strategy for improving medical outreach to a community with established health resources. With the partnership of the community health department at Chia-Yi Christian Hospital (CYCH), I developed an Android smartphone app to more efficiently streamline the health screening process and make this service more accessible to the community in Chiayi, Taiwan.

Currently, Taiwan is experiencing a growing shortage of primary care physicians; at the same time, it carries the burden of being one of the most rapidly aging societies. The elderly population rose to 11.2 percent in 2013 and is projected to reach 20 percent by 2025, 30 percent by 2040, and 40 percent by 2056. Meanwhile, the birth rate continues to decline while life expectancy increases. As the population structure in Taiwan undergoes drastic change in the near future, sustainable health care for the elderly will inevitably be of tremendous concern.

For an aging society like Taiwan, consistent management of and greater attention to personal health is key. Accordingly, I created a smartphone app for comprehensive health screening of chronic disease risk factors and other health concerns common to the elderly. The app modules include physical screenings for obesity (BMI and WHR), hypertension (SBP and DBP), and diabetes (BGL), in addition to standard medical questionnaires for depression (GDS), dementia (AD8 and MMSE), quality of life (WHOQOL-BREF), and activities of daily living (ADL), adapted to the Taiwanese culture. Results and recommendations are compiled in the final module, and the data can be stored in the cloud and readily visualized in table and graph form.

Furthermore, the app is designed to be implemented at the level of CYCH-affiliated community centers throughout the Chiayi county. Social workers staffed at these community centers would be trained in using the app to regularly screen visiting patients. This would eliminate the learning curve on the patient side, allow easy data integration with hospital EMR, and promote wellness programs available at the community centers. Overall, such an app would facilitate greater convenience for personal health management among patients in Chiayi and enhance the utility of external local health services within the CYCH system.

**Creating a Network of High Quality Skilled Nursing Facilities:
Early Experiences of an ACO in Post-Acute Care Quality Improvement**

Daniel E. Lage, MSc
Harvard Medical School, Francis Weld Peabody Society, Class of 2017

D. Clay Ackerly, MD, MSc
Division of General Internal Medicine (Geriatrics)
Massachusetts General Hospital

Background: Post-acute care (PAC) is a significant source of cost growth and variation in the Medicare program, and is key to Accountable Care Organization (ACO) efforts to improve value. Skilled Nursing Facilities (SNFs) are high cost and variable quality PAC providers, and they suffer from high readmission rates and insufficient care coordination. The integrated health system, Partners HealthCare (PHS) and its Pioneer ACO, launched the PHS SNF Collaborative Network (“the Collaborative”) in October 2013 in order to identify and partner with high-quality SNFs.

Methods: This study will describe the criteria that PHS used to create the Collaborative, and then will describe the characteristics of those SNFs that were evaluated under the criteria. This study also reports the results of a satisfaction survey sent to participating SNFs.

Results: PHS created a two-tier criterion for the Collaborative. First, facilities had to score greater than 125 (50th percentile) on the Massachusetts Department of Public Health score and had to have at least a three-star rating on the Centers for Medicare and Medicaid Services Five-Star scoring system. Second, a variety of self-reported criteria were used to define value in a way that would be useful to PHS patients. Out of 140 SNF’s that applied to the Collaborative, 82 (59% of applicants) met the initial criteria and 47 (34% of applicants) met the secondary criteria. SNF’s not meeting the minimum criteria, SNF’s meeting the minimum criteria but not selected, and selected SNF’s had average CMS Star Ratings of 2.7, 4.1, and 4.6, respectively, and average MA DPH ratings of 119, 128, and 129, respectively ($p < 0.01$ for all). Selected SNF’s were more likely to have greater than 5 days of clinical coverage (17.0% vs. 8.6% overall), and they were more likely to have a physician see patients within 24 or 48 hours (38.3% vs. 27.9% overall & 93.6% vs. 87.9% overall, respectively). There were minimal differences in EMR use and INTERACT use. Further, a survey of Collaborative SNFs found that SNF’s were highly satisfied with the Collaborative process (average satisfaction, 4.6/5, with 1=Very Dissatisfied and 5=Very Satisfied, $n=19$).

Conclusions: We find that self-reported measures can describe factors important for PAC quality and care coordination, and that SNFs found the Collaborative process valuable. Future studies should fully validate the Collaborative criteria and assess how this model can best guide a long-term process of partnering with SNFs to improve the value of PAC for ACO patients.

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**Retrospective Review of Acetaminophen/Diphenhydramine Overdose:
Features of Toxicity and Outcomes as Reported to California Poison Control**

Lucinda Lai
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Raymond T. Chung, MD
Gastroenterology, Department of Medicine
Massachusetts General Hospital

Acetaminophen and acetaminophen combination products are the medications most frequently involved in intentional and unintentional poisonings. *N*-acetylcysteine (NAC) is an effective antidotal therapy for the prevention and treatment of acetaminophen hepatotoxicity, but patients with massive ingestions and/or co-ingestions of drugs that slow gastric motility may have altered absorption kinetics that interfere with the applicability of the standard diagnostic nomogram and the 21-hour NAC treatment protocol. The anticholinergic effects of diphenhydramine may slow gastric motility, thus producing delayed absorption, a delayed peak in serum acetaminophen levels, and/or a second peak.

The first objective of this descriptive study was to characterize the patient demographics, clinical variables, and outcomes related to acetaminophen/diphenhydramine overdoses compared to acetaminophen overdoses. The second objective was to identify delayed peaks and second peaks of serum acetaminophen levels from acetaminophen/diphenhydramine overdoses compared to acetaminophen overdoses. The third objective was to assess the usefulness of the acetaminophen-transaminase multiplication product (APAPxAT) as a risk prediction instrument for hepatotoxicity after acute overdose. The fourth objective was to determine if patients developed hepatotoxicity despite initial presentation with undetectable acetaminophen levels and normal transaminase levels.

We retrospectively reviewed cases of acetaminophen/diphenhydramine overdose treated at a health care facility and reported to the California Poison Control System from 1997 to 2013. A total of 382 cases were reviewed: 93 cases of acetaminophen/diphenhydramine overdose that resulted in mild hepatotoxicity (peak transaminase greater than 100 but less than 1000 IU/L), and 126 cases of acetaminophen/diphenhydramine overdose that resulted in significant hepatotoxicity (peak transaminase greater than 1000 IU/L). We compared the latter group with 163 cases of plain acetaminophen overdose that resulted in significant hepatotoxicity. For each case, demographic and clinical variables were tallied, including patient age and gender, prior ethanol use, size of ingestion, serial acetaminophen levels, hepatotoxicity, peak measured International Normalized Ratio, time to NAC treatment, decontamination with activated charcoal, and outcomes.

We used a descriptive method and created a graphical representation of serial serum acetaminophen levels. The graph demonstrated that in cases of acetaminophen/diphenhydramine overdose, the serum acetaminophen levels did not fall as would be expected from a plain acetaminophen overdose. In the combination group, a late rise in acetaminophen levels was common.

Further analysis will include quantifying the time-to-peak for levels of acetaminophen; and qualitative descriptions of cases identified by the second, third, and fourth objectives of this study.

**Migration and HIV Risk Among Men Who Have Sex With Men, San Francisco,
2011**

Tenzing T. S. Lama
Harvard Medical School, William Bosworth Castle Society, Class of 2017

Wili McFarland, MD, PhD, MPH, TM
Center for Public Health Research/Department of Epidemiology and Biostatistics
San Francisco Department of Public Health/University of California, San Francisco

In the United States, men who have sex with men (MSM) are disproportionately affected by HIV and in San Francisco, they account for nearly 90% of HIV infections. While individual level behavior risks remain at the crux of the epidemic, they bespeak larger social, network, and structural risks – so called “risk contexts”- that contribute to HIV dynamics and consequently, have produced more effective intervention strategies than those focused solely on individual level risks. Increasingly, studies on migration - broadly defined in this study as changing one’s place of residence for time-limited stays or permanent settlement, and crossing a geographically-defined border - have postulated that migration-related structural factors could contribute to increased risks for HIV transmission for MSM who migrate to urban environments, yet empirical data is lacking.

In this study, we analyzed data from the National HIV Behavioral Surveillance System collected in 2011 to ascertain whether migration-related factors contributed to HIV infection, sexual risk, and health seeking behaviors among MSM in San Francisco, a gay epicenter. Men were eligible to participate if they were 18 years or older, lived within the San Francisco Bay Area, reported past male/male sexual behavior, able to provide verbal consent, and able to speak English or Spanish. Among the 510 MSM who completed the survey, HIV prevalence was 22.8%. We found that two central migration-related factors, immigrant status and time lived in San Francisco, were not related to condomless anal intercourse, recent HIV testing, recent STI testing, current health insurance or a recent health visit. Multivariable analyses demonstrate that while migration was not associated with increased risk for prevalent HIV infection, those who had lived in San Francisco for more than five years were at greater odds of being HIV-infected than those who had lived for less than a year (Adjusted OR, 3.54; 95% CI, 1.79-6.98) even after adjusting for age, race, income, education, and location of birth.

In addition to addressing individual and structural factors, our analyses suggest that migration status must also be considered to optimize HIV prevention strategies among MSM.

**Association of head and neck surgical outcomes
with surgeon and hospital financial incentives**

Bennett Lane

Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Sunil Eappen, MD

Department of Anesthesiology, Massachusetts Eye & Ear Infirmary

Amid a shifting landscape of payment models, elucidation of current financial incentives can inform transitional approaches to value-oriented payment strategies. The present study contributes novel information about the relationship of physician and hospital financial incentives to surgical outcomes for inpatient head and neck procedures.

A retrospective analysis of administrative ICD-9-CM codes and hospital accounting data was performed. The study population included all inpatients at a specialty hospital discharged between October 2010 and September 2013 who were admitted by hospital-employed head and neck surgeons, were charged for operating room time in the index (initial) admission, and had comprehensive data available.

The main outcome measure was surgeon revenue; additional outcome measures were hospital revenue, hospital total costs, hospital total margin, and hospital contribution margin. All measures were compared between patients with and without at least one complication. Patients were classified as having a complication if they received one of 9 pre-specified diagnoses indicating a complication after admission, returned to the operating room (OR), or were readmitted within 30 days of discharge. Financial outcomes were evaluated using a generalized multivariable linear regression.

1,176 surgical episodes were identified, comprising 1,363 admissions when including 30-day readmissions. 269 (23%) episodes included at least one surgical complication, with the most common being readmission (153 episodes; 13%) and return to the OR (73 episodes; 6%). Occurrence of any complication was associated with greater surgeon professional fees (\$1,190; $p < 0.0001$), greater hospital revenues (\$16,160; $p < 0.0001$), greater hospital total costs (\$26,240; $p < 0.0001$), and lower hospital total margin (-\$10,080; $p < 0.0001$). Subgroup analysis by type of complication demonstrated greater hospital contribution margin was associated with any readmission (\$2,830; $p < 0.05$) but lower hospital contribution margin was associated with any return to the OR (-\$6,590; $p < 0.0001$). Subgroup analysis by payer type demonstrated occurrence of any complication was significantly associated with greater contribution margin for Medicare-insured patients (\$2,430; $p = 0.02$); no significant association with contribution margin was found for patients covered by commercial insurance.

In conclusion, head and neck surgeons' financial interests are misaligned with optimal patient outcomes while hospital financial incentives are aligned on a total margin basis. Physician payment programs should better connect physician financial incentives to activities that improve patient care outcomes. Future work may address limitations of this study by incorporating data from additional medical centers, adding clinical validation of complications identified by administrative data, and by examining anesthesiology professional fees.

Early Beyond-the-self Purpose and Later Life Psychological Well-being**Amy Le****Harvard Medical School, Francis Weld Peabody Society, Class of 2017****Robert J. Waldinger, MD****Harvard Study of Adult Development, Department of Psychiatry
Massachusetts General Hospital**

Purpose has been defined as a stable and generalized intention to accomplish something that is meaningful to the self and of consequence to the world beyond the self (Damon et al., 2003). This study investigates whether purpose established in early adulthood is associated with psychological well-being in mid to late life (ages 50-70). It is hypothesized that individuals who manifest purpose in early adulthood want to make a difference in the world and will do so through prosocial behaviors that also contribute to greater personal well-being.

From 1939 to 1942, 268 Harvard College sophomores were selected to participate in the Study of Adult Development (Heath, 1945). Their lives were followed closely for over 70 years and documented through questionnaires administered every two years, physical exams every 5 years, and interviews every 15 years.

The summary of each participant's intake interview was analyzed and the presence of purpose was determined using a reliable coding system which identified a goal, actions taken to achieve that goal, and the degree to which the goal was of consequence beyond the self. Thus the men were divided into two groups: those who had purpose in college ($n=77$) and those who lacked purpose in college ($n=145$). Two coders coded 20% of records in common ($n=54$) and showed good agreement on the presence or absence of purpose ($\kappa=.79$, $p<.01$).

Men who manifested purpose during college were rated by research staff over 40 years later as having a better adjustment to aging at age 62 ($t=2.37$, $p=.02$), were involved in more social organizations between the ages of 50-70 ($t=2.09$, $p=.04$), and used alcohol less frequently as reported at age 53 ($t=2.13$, $p=.04$). Contrary to hypotheses, the two groups did not differ in their commitment to volunteer or charity work, church attendance, or income in mid to late life.

Findings confirm the hypothesis that development of beyond-the-self purpose in early adulthood is associated with greater psychological and social well-being 30-40 years later. Sharper focus on the development of purpose can move the field beyond the current catalogue of general psychological factors associated with midlife and late life health toward an understanding of specific factors that explain these links and may be targets for effective intervention that promote healthy aging.

Valproic acid is associated with improved survival in glioblastoma in a dose-dependent manner but worse outcome in lower grade gliomas

Andrew Q. Le

Harvard Medical School, Walter Bradford Cannon Society, Class of 2016

Brian Nahed MD

**Department of Neurosurgery
Massachusetts General Hospital**

INTRODUCTION: Valproic acid (VPA), a commonly used anti-epileptic drug (AED), acts as a histone deacetylase (HDAC) inhibitor. Since HDACs play a key role in epigenetic regulation of gene expression, HDAC inhibitors have been increasingly studied for their potential role in cancer therapy. Recent studies have shown that combining VPA with temozolomide (TMZ) can lead to improved survival in patients with GBM. In this retrospective study, we not only examined the effect of total dose of VPA on GBM survival, but also examined the effects of VPA in patients with lower grade gliomas.

METHODS: A retrospective analysis of 359 patients with high-grade and low-grade gliomas treated with temozolomide was conducted to evaluate the effects of VPA on progression and overall survival. The study analyzed the effect of VPA dose on progression-free survival (PFS), overall survival (OS), and malignant transformation of non-GBM lower grade gliomas.

RESULTS: After adjusting for biopsy, subtotal resection, gross total resection, multiple resections, and concurrent chemotherapy in an extended Cox model, VPA was associated with a 29% decrease in hazard of death within patients with GBM ($p=0.037$). Moreover, every 100g increase in VPA dose decreased one's hazard of death by 9% ($p = 0.005$) in GBM patients. Interestingly, VPA was associated with a 162% increase in hazard of progression in the lower grade non-GBM patients ($p = 0.004$) and every 100g increase in VPA dose increased one's hazard of progression by 8% ($p = 0.003$). When examining time to malignant progression, patients who took VPA had 2.17 times the hazard of progression to higher grade compared to those who did not take VPA ($p=0.020$).

CONCLUSION: Valproic acid was associated with improved survival in GBM in a dose dependent manner. However, in lower-grade gliomas VPA was associated with higher rate of malignant progression and decrease in PFS. Prospective evaluation of VPA in glioblastoma and lower-grade gliomas is warranted to confirm these findings.

Age-Dependent Effects of Propofol on Frontal Electroencephalogram Power and Coherence**Johanna M. Lee****Harvard Medical School, Irving M. London Society, Class of 2017****Emery N. Brown, MD, PhD and Patrick L. Purdon, PhD****Department of Anesthesia, Critical Care and Pain Medicine****Massachusetts General Hospital**

Frontal electroencephalogram (EEG) patterns observed during propofol-induced unconsciousness consist of a combination of large amplitude slow-delta oscillations (0.1-4 Hz) and coherent alpha oscillations (8-13 Hz). However, these patterns have not been studied in pediatric patients and cannot be used to reliably guide anesthetic administration. Because the nervous system is in a dynamic state of change during childhood and adolescence, we investigated age-related changes in EEG power spectra during propofol sedation. Specifically, we sought to test the hypothesis that frontal EEG slow-delta and alpha oscillation power exhibit age-related fluctuations.

We recorded 4-channel EEG data using the SEDLine (Masimo, Irvine, CA) monitor during the routine care of patients (propofol-induced unconsciousness) between 0 and 28 years of age (n=111). We dichotomized patients into the following age groups: group 1 (2-4 yrs), group 2 (5-8 yrs), group 3 (9-12 yrs), group 4 (13-16 yrs), group 5 (17-20 yrs), and group 6 (21-28 yrs). We analyzed the EEG using multitaper spectral and coherence analysis, and coherence was estimated between frontal channels F7 and F8. Average power was calculated from the EEG spectrum of each patient within the following frequency ranges: slow-delta (0.1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-20 Hz), and gamma (20-40 Hz). We compared the power spectra using the Kruskal-Wallis followed by Dunn's method for post-hoc analysis.

When we analyzed the spectra, we found that EEG slow-delta oscillation power was largest in group 2 (mean±SD; power, 18.59dB±3.18), followed by group 3 (18.50dB±3.18), group 4 (16.69dB±2.92), group 5 (14.43dB±3.03), group 1 (12.82dB±5.31), and group 6 (11.75dB±3.45). In particular, groups 5 and 6 had significantly lower slow-delta oscillation power than groups 2 and 3 (p<0.05). We also found that alpha oscillation power was largest in group 2 (10.41dB±1.90), followed by group 1 (10.27dB±3.30), group 3 (9.93dB±2.82), group 4 (6.53dB±4.18), group 6 (4.58dB±4.52), and group 5 (4.21dB±3.12). In particular, group 5 had significantly lower alpha oscillation power than groups 1, 2, and 3 (p<0.05). In addition, preliminary data in patients under 2 years of age (n=6) showed propofol-induced slow-delta oscillations, but not alpha oscillations, at 4 months of age, with the appearance of alpha oscillations at 5 months of age. However, these alpha oscillations were not highly coherent before 17 months of age.

Our results show age related changes in the EEG power spectra and coherence during propofol-induced unconsciousness. Slow-delta oscillation power and alpha oscillation power were larger in children than in adults, likely explaining why existing depth-of-anesthesia monitors are unreliable in the pediatric population. In addition, preliminary data show changes in EEG structure and coherence in patients under 2 years of age. The absence of coherent alpha oscillations in infants may suggest that the thalamocortical loop implicated in propofol-induced unconsciousness is not yet fully developed, and higher anesthetic concentrations may be required to maintain unconsciousness in infants. Our results suggest an age-specific strategy for monitoring brain states under anesthesia in pediatric patients. Overall, the age-dependent EEG differences in power spectra and coherence likely reflect ongoing neurological processes like myelination and neural pruning. Further investigation will help establish the precise correspondence between the structure of EEG oscillations and neurological development.

Tumor Genotype and Toxicity Risk in Glioblastoma**David J. Lee****Harvard Medical School, Walter Bradford Cannon Society, Class of 2017****Patrick Y. Wen, MD****Center for Neuro-Oncology, Dana-Farber/Brigham & Women's Cancer Center****Nils D. Arvold, MD****Department of Radiation Oncology, Dana-Farber/Brigham & Women's Cancer Center**

Glioblastoma (GBM), the most common primary malignant brain tumor, has a poor prognosis and causes significant morbidities. For example, seizures are seen in approximately 50% of patients, and venous thromboembolism (VTE) affects up to 30% of patients within 1 year of surgery. With extensive genomic characterization of GBM revealing marked heterogeneity between tumors, molecular mechanisms underlying specific GBM-related toxicities have recently been proposed. For example, *EGFR* amplification has been purported to increase the risk of VTE through tissue factor upregulation. Also, *IDH1* mutation may increase risk for seizures via the accumulation of 2-hydroxyglutarate, an oncometabolite that is structurally similar to glutamate and thus can cause excitotoxicity by activating NMDA receptors. Yet it remains to be determined whether such tumor molecular markers can be used clinically to predict risk of morbidity. The purpose of this study was to investigate the correlation between GBM genotypes and GBM-associated morbidities.

We conducted a retrospective review of 178 GBM patients diagnosed between 1998-2013 and treated at Dana-Farber/Brigham & Women's Cancer Center, assessing for incidence of seizures, VTE, and other toxicities, in addition to baseline patient, tumor, and treatment characteristics. We also analyzed molecular profiling results from additional pathologic testing of their GBM from the Brigham & Women's Hospital Center for Advanced Molecular Diagnostics. These data included array comparative genomic hybridization (OncoCopy, n=104), mass spectrometry-based mutation genotyping (OncoMap, n=79), targeted exome sequencing of 275 known cancer genes (OncoPanel, n=52), chromogenic in situ hybridization (n=77), and immunohistochemical staining (n=130).

Reviewing these complementary assays and patient clinical data, we observed that patients with *IDH1*-mutant GBM were significantly more likely to have seizure during their adjuvant chemoradiation phase, compared to patients without an *IDH1*-mutant GBM (OR=3.4, p=0.04). No significant correlation was found for *EGFR* amplification and VTE, when comparing *EGFR* amplified and *EGFR* non-amplified tumors (OR=0.64, p=0.27). Multivariable testing is ongoing. Correlations between other genotypes, including *MGMT*, *PTEN*, and *PDGFRA*, and various toxicity outcomes, including seizures, VTE, thrombocytopenia, and leukopenia, were also assessed in an exploratory analysis.

This report demonstrates the feasibility of advanced molecular testing of GBM samples to correlate tumor genotype with toxicity outcomes. Our univariable results suggest a relationship with *IDH1* mutations and seizure, and no relationship between *EGFR* amplification and VTE. These preliminary findings hold the potential to provide targeted prophylactic therapies to patients with tumor genotypes predisposing them to specific toxicities related to treatment and/or the tumor itself, for improved clinical outcomes.

**5-Hydroxymethylcytosine Expression in Metastatic Melanoma versus Nodal Nevus
in Sentinel Lymph Node Biopsies**

Jonathan J. Lee

**Harvard Medical School, Oliver Wendell Holmes Society, Class of 2015
Post-Junior Fellowship in Pathology & Dermatopathology, Brigham and Women's
Hospital**

Christine G. Lian, MD

**Program in Dermatopathology, Department of Pathology
Brigham and Women's Hospital**

Sentinel lymph node biopsies are conducted to stage patients with newly diagnosed melanomas that have histopathological attributes conferring defined levels of metastatic potential. Because benign nevic cells may also form 'deposits' in lymph nodes (nodal nevus), the pathological evaluation for metastatic melanoma within sentinel lymph nodes can be challenging.

Twenty-eight sentinel lymph node biopsy cases containing either metastatic melanoma (N=18) or nodal nevi (N=10) were retrieved from the archives of the Brigham and Women's Hospital, Department of Pathology (2011-2014). In addition, two sentinel lymph node cases that were favored to represent metastatic disease but whose histopathological features were viewed as equivocal, with melanoma favored, were also included. Dual labeling for the melanocyte lineage marker, MART-1, and the epigenetic marker, 5-hydroxymethylcytosine, a functionally significant indicator that has been shown to distinguish benign nevi from melanoma, was performed on all cases using immunohistochemistry and/or direct immunofluorescence.

All (18 of 18) metastatic melanoma cases showed complete loss of 5-hydroxymethylcytosine nuclear staining in MART-1-positive cells, and all (10 of 10) nodal nevus cases demonstrated 5-hydroxymethylcytosine nuclear staining in MART-1-positive cells. In addition, 5-hydroxymethylcytosine staining confirmed the favored diagnoses of metastatic melanoma in the two 'equivocal' cases.

Thus, 5-hydroxymethylcytosine may be a useful adjunctive marker to distinguish between benign nodal nevi and metastatic melanoma during the evaluation of sentinel lymph node biopsies for metastatic melanoma. Additional cases of equivocal sentinel lymph node biopsies deserve further study to determine whether this biomarker may be useful in such a setting.

Towards a Simple Oncology Electronic Health Record for Low and Middle Income Countries: Lessons from Zamni Lasante in Mirebalais, Haiti

Sean Legler

Harvard Medical School, William Bosworth Castle Society, Class of 2017

Lawrence Shulman, MD

**Director of the Center for Global Cancer Medicine
Dana-Farber Cancer Institute**

Despite the existence of effective therapies for many cancers, oncology treatment programs have so far failed to make major inroads into many of the world's low and middle income countries (LMICs). The global inaction is in part fueled by concern over what some perceive as insufficient evidence for efficacious, well-coordinated, cost-effective cancer care in low-income settings. Generating a broader base for such evidence will be crucial to turning the tide in favor of expanding global oncology treatment.

To make this possible, information technology systems have the potential to both enable high quality care in LMICs and to simultaneously monitor and evaluate the care being delivered. However, while the electronic health record (EHR) is well established as a valuable tool for treating and tracking cancer patients in high-income countries, it is less clear how this tool should be intelligently used in LMICs, which have different sets of needs and capacities.

In order to improve, assess, and demonstrate the efficacy of a cancer care program at a Partners in Health hospital in Mirebalais, Haiti, we sought to (i) analyze the benefits and challenges associated with an oncology EHR in an LMIC setting, (ii) identify current clinical and reporting needs of the cancer program in Mirebalais and (iii) to design a simple electronic health record to meet these needs. In doing so, we drew upon experience implementing a cancer care information system designed and built for Butaro Cancer Center in Rwanda, as well as upon long-standing experience in oncology EHRs at Dana-Farber Cancer Institute in Boston, MA.

To accomplish our aims, we first identified a set of basic data elements to collect for the cancer program. This included necessary demographic, diagnostic, therapeutic, outcome, and follow-up data for each patient. We then spent time on-site at Mirebalais to map current workflows and pathways of care. Interviews with clinicians and staff helped refine clinical and reporting goals according to local needs. Finally, we developed a prototype EHR customized for the program.

This simple oncology EHR enables comprehensive patient overviews, ongoing clinical updates, scheduling, biopsy tracking, toxicity assessments, outcome monitoring, and multiple real-time graphical dashboards for program coordination and quality of care evaluation. Additionally, it may help facilitate the organization of a larger scale cancer registry. Moving forward, the prototype EHR will be used for retrospective data collection, iteratively improved, assessed for limitations, and tested in clinical scenarios in December 2014.

Assessment of the Fetal Thymus in Normal Fetuses and in Fetuses with Congenital Heart Defects: Comparison of Two Sonographic Techniques

Joshua I. Leibowitz

Harvard School of Dental Medicine, Walter Bradford Cannon Society, Class of 2017

**Elena Sinkovskaya, MD, PHD
Maternal Fetal Medicine Department
Eastern Virginia Medical School**

The thymus is an essential part of the adaptive immune system of the fetus, which grows rapidly in utero to reach its greatest size. This can be seen utilizing high-resolution ultrasound and in examining fetuses with impaired thymic growth. A hypoplastic fetal thymus is typically found in association with deletion 22q11 (del.22q11), but a small thymus has also been reported in fetuses with intrauterine growth restriction (IUGR), prematurity and related chorioamnionitis and pre-eclampsia. Previously, the thymus has been difficult to measure by ultrasound. Attempts have included anterior-posterior thickness measurements; however, these have been difficult to reproduce since the great vessels tend to vary in size, especially in patients with congenital heart defects. The aim of this study was to compare the commonly used Three Vessel Trachea view and the recently proposed Left Brachiocephalic Vein view to assess thymus size. Ultimately, we compared the intra- and inter- observer reproducibility in TT-ratio calculations using these two different ultrasound views. While the great vessels inhibit the ability to reproducibly measure the thymus in the Three Vessel Trachea View in fetuses with cardiac anomalies, the Left Brachiocephalic Vein stays fairly constant. Therefore, we propose that the Left Brachiocephalic Vein view, a view in which the thymus is apparent, will allow for more accurate and reproducible TT-ratio measurement.

The study population consisted of 200 prenatal ultrasounds without any cardiac abnormalities and 50 prenatal ultrasounds with confirmed cardiac abnormalities. These ultrasound exams were collected retrospectively and were performed between 11+0 and 39+6 weeks. The echocardiographs were obtained using GE Voluson machines. The two views studied were the Three Vessel Trachea View (3VT) and the Left Brachiocephalic Vein View (LBCV). The 3VT was obtained by first measuring the distance between the posterior vessels and the anterior sternum. Subsequently, the distance between the sternum and the spine was measured. These two were measured in a Thymic-Thoracic ratio (TT-ratio), which is the ratio between the thymus diameter and the intrathoracic diameter.

After evaluation of 200 normal fetuses, the Thymic-Thoracic ratio for both the LBCV and 3VTV views did not have statistically significant changes as gestational age increased. For the LBCV TT-ratio, the average was $.4119 \pm .068$. The LBCV Thymic A-P average was 9.645 ± 1.808 .

The plan for the remainder of the analysis is to calculate both the intra-observer variability as well as the difference in the TT-ratio for both the LBCV and the 3VTV for fetuses with cardiac abnormalities.

The Effect of Delayed Gastric Emptying on the Thermic Effect of Food (TEF)**Stephanie Lin****Harvard Medical School, Walter Bradford Cannon Society, Class of 2017****Eleftheria Maratos-Flier, MD****Division of Endocrinology****Beth Israel Deaconess Medical Center**

The thermic effect of food (TEF) is defined as the postprandial increase in energy expenditure associated with digestion, absorption, and storage of nutrients. It accounts for up to 10% of total energy expenditure in humans. We discovered in an ongoing parent study that subjects receiving 10mcg of the GLP-1 agonist exenatide demonstrated blunting of TEF. Since exenatide is known to delay gastric emptying, we hypothesized that the slower transit of food reduces intestinal absorption rate and consequently abrogates TEF. Currently, the effect of delayed gastric emptying on TEF is unknown.

The two aims of this study were to: 1) determine the effect of delayed gastric emptying on TEF, and 2) compare the changes in TEF induced by exenatide vs. morphine, an agent known to delay gastric emptying to a similar degree. To date, we recruited and studied 6 non-diabetic obese women (mean age 38, mean BMI 33.97) who had completed the parent study with metabolic measurements before and after treatment with exenatide or placebo. Resting metabolic rate (RMR) was measured by indirect calorimetry after overnight fasting per the parent study protocol. Subjects then received 0.05 mg/kg IV morphine followed by 250cc of Boost® liquid meal. RMR was repeated 1, 2, 3, and 4 hours postprandially. One subject was discontinued at 2 hours due to nausea and vomiting.

After morphine administration, mean TEF peaked at 3 hours postprandially compared to 1 hour without morphine. Although maximum TEF was reduced with morphine compared to baseline (210.2 ± 98 kcal vs. 231 ± 38 kcal), this difference was not statistically significant ($p=0.88$, Student's paired t-test). Among the subjects who were treated with exenatide in the parent study and demonstrated blunted TEF ($n=2$), maximum TEF was 16 ± 47 kcal after exenatide compared with 262.5 ± 192 kcal after morphine (not statistically significant, $p=0.49$, Student's paired t-test).

Our study is currently limited by the small sample size, but we plan to continue recruitment throughout the fall and winter. We are also limited by the assumption that morphine is truly delaying gastric emptying in our subjects. Future studies should directly measure gastrointestinal transit time as well as TEF. Nonetheless, the preliminary trends suggest that morphine delays gastric emptying as expected, with peak TEF occurring approximately 2 hours later than without morphine. However, we did not observe the prolonged blunting of TEF with morphine as we did with exenatide. This indicates that exenatide may affect TEF through a different mechanism than delayed gastric emptying.

**A Needs Assessment of Family Planning among the Ngöbe–Buglé of Bocas Del Toro,
Panama**

Mckenna M. Longacre
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Kim Wilson MD, MPH
Departments of Pediatrics and Global Health
Boston Children's Hospital

Panama is home to approximately 153,000 indigenous people, collectively referred to as the Ngöbe–Buglé. Spanning an archipelago and mountainous mainland, the northeastern province of Bocas Del Toro is home to approximately half the Ngöbe–Buglé population. The World Bank has characterized poverty in indigenous areas of Panama as “abysmal:” 95% of people live below the poverty line. To help address health needs, the American NGO Floating Doctors recently began providing free care to select communities. Recent field experience has led Floating Doctors to hypothesize that lack of access to family planning negatively impacts the Ngöbe–Buglé communities.

To better understand the need for and barriers to family planning among the Ngöbe–Buglé, we conducted quantitative and qualitative needs assessments among the Floating Doctors patient population. We collected 72 quantitative surveys modeled after the Department of Health Services Individual Questionnaire as well as 41 interviews of key informants using open-ended questions to characterize community family planning needs, norms, and preferences. Key informants included representative community members, Peace Corps and Red Cross workers, and Floating Doctors staff.

Indigenous interviewees reported wanting fewer children (2.5, range 1-11) than the average for Ngöbe–Buglé households in the region (4.6). In terms of ideal number of children, no significant difference ($p=0.401$) was detected between men (median 3, range 1-11) and women (median 2.5, range 2-7). Yet it was found that 48% (25/52) of sexually active, reproductive-age women who did not want more children used no birth control. Lack of access to family planning was the most common reason cited for non-use. This contrasts with opinions of non-indigenous key informants, who suggested that regional preferences for larger families might pose barriers to contraception use.

A common theme among indigenous informants was that with increased access to family planning, young women may be less likely to become pregnant immediately following menarche. Young motherhood was identified as the greatest local barrier to accessing education, healthcare, and economic share.

This preliminary assessment suggests that increased access to family planning is needed among and acceptable to the Ngöbe–Buglé. Indeed, access to family planning may be prerequisite to addressing other disparities among Panama's indigenous people. Particularly as Panama's economy grows so quickly, if the Ngöbe–Buglé are to participate in economic development and sustain their autonomy, access to family planning should be expanded.

Characterizing the Effect of HIV Infection on the Human Gut Microbiome**Jesús Mario Luévano Jr.****Harvard Medical School, Irving M. London Society/HST, Class of 2017****Douglas S. Kwon, MD, PhD****Assistant Professor in Medicine, Ragon Institute****Massachusetts General Hospital**

UNAIDS estimates approximately 34 million people worldwide are infected with Human Immunodeficiency Virus (HIV). In the absence of antiretroviral therapy (ART), HIV leaves the body susceptible to many potentially fatal opportunistic diseases. The human gut microbiome has been shown to be key in the regulation of the host's immune system and metabolism and yet the effect of HIV on enteric microbial communities remains unclear. Deregulation of complex community structure is demonstrated in many of the pathologies related to HIV infection including metabolic disorders, chronic inflammation, and susceptibility to opportunistic infections. Past work on SIV-infected nonhuman primates found mild microbial changes, but significant virome expansions. A recent exploratory human trial found that chronic HIV infection did have long-term effects on the community composition.

To better understand the progression of HIV and its effect on the host's immune system, we will study differences between intestinal microbiome composition, community gene expression, and mucosal tissue of patients in the U.S and sub-Saharan Africa who are HIV infected (untreated, ART-treated, and controllers) or uninfected. We hypothesize that there will be significant shifts in the microbiome composition and genes expressed in these cohorts, and that these shifts will associate with the host's status. In addition, being able to compare samples from patients in Boston and Uganda provides a greater perspective of the impact of HIV infection.

To quantify this difference we extracted Total Nucleic Acid (TNA) from the 123 collected patient fecal samples. We then extracted total DNA and RNA separately for sequencing and subsequent analysis of the microbial composition, and the transcriptome. Using the DNA, a library of 16S amplicons was created via PCR amplification for sequencing. Data analysis will include trimming of the reads, removal of host or low-quality sequences, and comparison to known sequences to establish Operational Taxonomic Units, based on >97% identity, using QIIME.

Future work will involve the use of total DNA and RNA for shotgun sequencing to gain further insight regarding gene presence/expression and community structure at the species level. We will additionally investigate the interrelationships between host immunity, HIV infection, and commensal microorganisms, all of which can influence prognosis and contribute to pathogenesis. We will use these analyses to better characterize HIV progression and to better understand the immunological landscape of the gut-associated lymphoid tissue and the down-stream repercussions of HIV infection on commensal microbial communities.

**Transposon Screen for Identification of Mechanisms of Resistance in
Medulloblastoma****Ethan MacKenzie****Harvard Medical School, Irving S. London Society, Class of 2017****Rosalind Segal MD, PhD****Department of Cancer Biology****Dana Farber Cancer Institute**

Medulloblastoma (MB) is the most common malignant brain cancer in children, with an incidence of 2 people per million per year. Combined modality treatment, involving surgical resection followed by radiation and chemotherapy, has reduced childhood disease mortality to around 25%. Unfortunately, 20 to 30 percent of successfully treated children will relapse. Furthermore, combined modality treatment is not without severe complications, including neurocognitive impairment and endocrine abnormalities.

One third of all MBs are caused by mutations that activate the hedgehog (Shh) pathway, mediated through activity of the Gli family of transcription factors. Recently inhibitors targeting smoothened (Smo), a component of the Shh receptor, have been shown to be effective in treating some Shh-subtype MBs. However, remission achieved with treatment with Smo inhibitors can be transient, and relapse with inhibitor-resistant disease often occurs in a matter of months. Furthermore, a significant proportion of Shh-subtype MB is resistant to Smo inhibitors even at the time of presentation. Thus far, examination of smoothened inhibitor resistant medulloblastoma reveals diverse mutations in Smo or in components further downstream in the hedgehog pathway, illustrating the need for a better understanding of the evolution of drug resistance in MB.

In order to elucidate mechanisms of resistance in Shh-subtype MB, members of our lab derived MB cell lines from tumors in *Ptc*^{+/-} mice. These cell lines were then mutagenized with *piggyBac* transposon designed by our lab capable of conferring gain or loss of function mutations. Approximately 400 clones resistant to Smo inhibitors LDE225 or Vismodegib were generated and the specific mutations identified using Nextgen Sequencing.

Of the resistant clones isolated, half possess mutations in the Suppressor of Fused (SuFu), a negative regulator of the hedgehog pathway, downstream of Smo, which has already been strongly tied to drug-resistance in MB, validating our screening methodology. Interestingly, the screen also isolated several mutations in genes coding for components of the primary cilium. These screen hits were validated through excision of transposon cargo and resultant restoration of a non-resistant phenotype in mutant lines.

Many steps in hedgehog pathway signaling take place in the primary cilium. Currently, we are investigating how mutations in particular primary cilium components alter subcellular localization, phosphorylation state, and function of the Gli proteins. Identification and elucidation of mechanisms of resistance in MB will provide valuable insight into how cancers evolve and allow for identification of possible therapeutics.

**Survival and prognostic factors for intracranial ependymomas in children: a report
of the Pediatric Brain Tumor Center at Dana-Farber Cancer Institute/ Boston
Children's Hospital**

**Amanda Marinoff
Harvard Medical School, William Bosworth Castle Society, Class of 2017
Alexandra J. Miliotis Fellowship in Pediatric Oncology**

**Mark W. Kieran, MD, PhD
Pediatric Brain Tumor Center
Dana-Farber Cancer Institute**

Ependymoma is the third most common brain tumor in children, accounting for 6-10% of all intracranial tumors. Unlike other primary brain tumors, factors that influence outcomes for pediatric patients with ependymomas are not well defined. To date, research has not yielded consistent findings with regard to the prognostic significance of common predictive factors such as age, extent of resection, tumor location, and pathology.

Although there are many studies of patients with intracranial ependymoma, relatively few have reported a large, single-institutional pediatric population with long-term follow-up. Many studies follow patients over relatively short periods of time, reporting 3-year, 5-year and more rarely, 10-year survival outcomes. Based on these data, the prognosis for children treated with current therapeutic standards for intracranial ependymoma is thought to be relatively favorable. In this study, analysis of 10-year and 20-year survival outcomes over the longest follow-up period to date calls into question this basic assumption provides insight into the long-term recurrence patterns of pediatric ependymoma.

Medical records were reviewed of 52 patients younger than 18 years who were diagnosed with and treated for WHO Grade II or Grade III intracranial ependymoma at the Pediatric Brain Tumor Center at Dana-Farber/Boston Children's Cancer and Blood Disorders Center between June 1985 and October 2002. Actuarial overall survival (OS) and progression-free survival (PFS) were determined by the Kaplan-Meier method. Univariate and multivariate analyses were performed using the log-rank test and Cox proportional-hazards models to evaluate the prognostic significance of age, gender, tumor location, extent of resection, tumor grade, and several histopathological features.

With a median follow-up of 13.6 years, the 5-year, 10-year, and 20-year overall survival (OS) rates were 61%, 53%, and 38%, respectively. The 5-year, 10-year, and 20-year progression-free survival (PFS) rates were 42%, 28%, and 24%. Only extent of surgical resection correlated with improved OS, while no factors were found to be significantly associated with PFS.

Amid the mixed literature regarding the prognostic factors for pediatric ependymoma, this study underscores the need to expand our scope beyond traditionally considered prognostic factors, such as pathological grade and tumor location. Additionally, our findings of high recurrence rates and relatively poor OS outcomes beyond the 5-year post-treatment mark indicate that it behooves us to follow ependymoma patients over longer periods of time and to reconsider the efficacy of current treatment paradigms.

Tracking Changes in Food Purchasing Behavior in Response to a Cooking-Centered Lifestyle Intervention

Benjamin Matthews
Harvard Medical School, Holmes Society, 2017

David Eisenberg, MD
Samueli Institute & Harvard School of Public Health, Department of Nutrition

People who spend more time preparing food tend to have lower BMIs, but only half of US households prepare food any given night. If barriers keeping people from cooking nutritious food at home were overcome – e.g., by teaching people to cook fast, inexpensive, pleasurable meals – then they may cook more, consume fewer processed foods, and/or experience improved quality of life and health.

A multi-disciplinary, educational intervention was developed and implemented as a pilot study, offering 16 weeks of training in cooking and nutrition, exercise, and mindfulness practices to 40 non-culinary employees of the Culinary Institute of America. The pilot study's purpose was to determine whether the intervention was feasible, reproducible, and effective for improving health.

To develop a fuller picture of the intervention's effectiveness, changes in participants' food purchasing behavior were analyzed using grocery receipts collected before, during, and after the intervention. Receipts and prices were transcribed into a database. Item listings were decoded, identified as food/nonfood, categorized, and assessed for levied taxes or discounts. Healthier food categories included foods like lean meats, whole grains, and minimally processed fruits and vegetables; less healthy foods included categories such as red meats, refined grains, sugar-sweetened beverages, and processed foods. Amounts spent in various categories were found for each participant and then aggregated to find overall trends in food spending.

Although this pilot study was not explicitly powered to detect statistically significant results, some trends were elucidated. The percentage of food spending in healthier food categories tended to increase (means – baseline: 31%, midpoint: 37%, endpoint: 51%), while spending in less healthy categories decreased (28%, 23%, 18%). In addition to increasing healthy food purchasing and decreased unhealthy food purchasing, food purchasing related to dining out fell during the intervention (27%, 14%, 11%). These results from 434 receipts support the idea that people who participate in this intervention become more likely to purchase healthier foods.

Limitations for this study are the 1-week receipt collection periods that might not accurately represent overall food spending, inability to decode a small percentage of receipt listings, and contingency on people's compliance with turning in all food receipts.

Future directions include investigating whether these changes are sustained beyond the intervention or examining whether larger changes in food spending correlate with larger changes in health measures like weight or blood pressure.

The Impact of Surgery on Upper Extremity Specific Disability in Patients with Thumb Osteoarthritis

Michal McDowell

Harvard Medical School, Francis Weld Peabody Society, Class of 2017

Dawn LaPorte, MD

Department of Orthopaedic Surgery

Johns Hopkins Medicine

The trapeziometacarpal (TMC) is one of the joints of the hand most frequently affected by arthrosis and is the most commonly operated site in the hand for arthritis. TMC osteoarthritis (OA) is an almost universal part of human aging and may cause pain, weakness, and disability. Patients who present with TMC arthrosis-related symptoms can consider operative and nonoperative treatment options. Given the high prevalence of TMC OA with age, the substantial variation in associated pain and disability, and the marked variation in physician treatment of TMC OA, it is important to generate evidence regarding upper extremity function to help the patient make an informed decision between nonoperative versus operative treatment.

Using a matched retrospective cohort study design, we will:

- 1) Examine the differences in patient reported upper extremity specific (UES) disability in patients with symptomatic TMC OA who choose operative treatment compared to patients who choose nonoperative treatment.
- 2) Identify the degree to which extremity specific disability following treatment is explained by psychological factors (e.g. pain interference or depression).

Our primary null hypothesis is that patients with symptomatic TMC OA who received operative treatment will have comparable disability compared to patients who received nonoperative treatment. Our secondary null hypothesis is that pain interference and depression are not associated with UES disability among patients with symptomatic TMC OA.

Eligible patients are being sent recruitment letters describing the scope of the study and three Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaires (upper extremity physical function, pain interference, and depression) for patient reference.

After the team receives an opt in agreement from prospective participants, the team is reaching out to patients to answer any questions, assess interest in study participation, and, if applicable, conduct an oral informed consent. Dr. Dawn LaPorte (PI) is also recruiting patients in clinic.

After data collection completion, we will match the 52 participants for the operative treatment group to the non-invasive treatment group by demographic factors. We also plan to match based on radiograph severity (using the Eaton-Litler-Burton classification scale) to allow more effective measurement of the actual impact of operative versus nonoperative treatment on quality of life among participants (and reduce the confounding by indication). We will look for determinants of PROMIS upper extremity disability in bivariable and multivariable statistical analyses.

Potential limitations include participant recruitment, questionnaire administration, confounding by indication, and complications in inclusion/exclusion criteria.

**Osteochondritis Dissecans of the Knee in Pediatric Baseball and Softball Catchers
Shows Increased Prevalence and Unique Location**

Mark J. McElroy

Harvard Medical School, Walter Bradford Cannon Society, Class of 2017

**Mininder S. Kocher, MD, MPH
Division of Sports Medicine
Boston Children's Hospital**

Background: Osteochondritis dissecans (OCD) of the knee is a condition that often leads physicians to recommend against at-risk children playing baseball/softball catcher. Multiple etiologic theories have been proposed.

Purpose: To determine whether clinical evidence supports (1) the recommendation to avoid playing catcher and (2) the etiologic theory of repetitive overuse and microtrauma.

Hypothesis: Children playing catcher are more likely to develop lesions, and these lesions are more likely to be in a posterior location than in children who play non-catcher positions.

Methods: Medical records from 1990-2014 of a tertiary care center were searched to find patients who had OCD of the knee, played baseball/softball at the time of presentation, had a specified field position, and had magnetic resonance imaging. Ultimately, 98 knees (78 patients) were identified: 33 knees (29 patients) in catchers and 65 knees (49 patients) in non-catchers. Points of comparison to test the first hypothesis were position played (catcher/non-catcher), demographics (age, unilateral/bilateral, and gender), and lesion severity by Hefti stage. Points of comparison to test the second hypothesis were sagittal and coronal lesion location.

Results: When compared to non-catchers, catchers were more likely to present with knee OCD ($P=0.001$) and presented at a younger age ($P=0.035$) but were similar with respect to bilateral involvement ($P=0.115$), gender ($P=0.457$), and lesion severity ($P=0.484$). Thus, the recommendation for at-risk children to avoid playing catcher was supported. When compared to lesions in non-catchers, lesions in catchers were more posterior on the femoral condyle ($P=.004$) but similar in coronal location ($P=0.210$). Combined with the biomechanics of squatting in the catcher position, this finding lends support to the repetitive overuse and microtrauma theory.

Conclusions: Catchers had a higher risk of developing OCD of the knee at a younger age than baseball/softball participants playing other positions. The posterior location of lesions in catchers may be the result of the repetitive stress placed on that aspect of the condyle. Recommendations to avoid playing catcher can now be considered evidence-based medicine.

Limitations: First, six of the twenty-nine catchers also reported playing non-catcher positions. This number of players is likely small enough to not skew the findings. Second, many young athletes play several sports. Although this diversity precludes isolating catcher status as the only predictor variable, participation in other high risk sports is likely spread evenly across both the catcher and non-catcher cohorts, minimizing the potential confounding effect of participation in multiple sports.

Changes in depressive symptoms after initiating antiretroviral therapy among HIV-positive patients in rural Uganda

Megan M. McLaughlin, MPH
Harvard Medical School, Walter Bradford Cannon Society, Class of 2017

Alexander Tsai, MD
Center for Global Health and The Chester M. Pierce, MD Division of Global Psychiatry
Massachusetts General Hospital

A high prevalence of depression has been documented among HIV-positive individuals in a variety of settings, including sub-Saharan Africa. Depression has important implications for outcomes in HIV patients. Depressive symptoms are associated with lower adherence to antiretroviral therapy (ART), accelerated HIV disease progression, and a higher risk of mortality. Several previous studies have documented reductions in depressive symptoms following initiation of ART. No study to date, however, has examined the trend in depressive symptoms across more than two years of follow-up after ART initiation. It is unclear, therefore, whether the changes in depressive symptoms observed over the short term are sustained over the long term.

Using data from a prospective cohort study, we sought to determine the extent to which patients' time on ART is associated with changes in depressive symptoms. We analyzed data from 637 HIV patients who initiated ART in rural Uganda between 2005 and 2012. Our primary outcome was depression symptom severity as measured by a 16-item modified Hopkins Symptom Checklist for Depression (HSCL-D). We fit three different generalized estimating equation models specifying HSCL-D score as the dependent variable and examining time on treatment as: (1) a continuous variable, (2) a continuous variable plus a quadratic term, and (3) a series of binary variables indicating each three-month period. In order to determine which of the three models best represents the data, we examined goodness of fit with QIC.

At the time of ART initiation, 206 (33%) of patients met screening criteria for probable depression (HSCL-D score ≥ 1.75). Participants were followed for a median of 5.2 years after ART initiation. We found evidence of a decline in average depression scores with increasing time on ART. Depression scores declined rapidly in the first six months following ART initiation, followed by a more gradual decline over the subsequent 18 months and a leveling off around the end of the second year on ART. QIC inspection indicated that modeling time on ART as a continuous variable provided the best fit.

Our results confirm findings from previous studies showing a decline in depression following ART initiation. Using data from patients prospectively followed for up to seven years after ART initiation, we document persistent reductions in depression symptom severity. However, after the first two years of improving symptoms, little further change was observed. These results provide additional support for the importance of expanding timely access to ART for patients living with HIV.

Does candidal carriage correlate with the development of oral candidiasis after topical immunosuppressive therapy?

Sara Meghji

Harvard School of Dental Medicine, William Bosworth Castle Society, Class of 2017

**Sook-Bin Woo, DMD, MMSc, FDSRCS (Edin)
Department of Oral Medicine and Dentistry
Brigham and Women's Hospital**

Oral candidiasis is the most common opportunistic infection of the oral cavity and results from the overgrowth of *Candida albicans* after an alteration of the local oral environment or from systemic use of antibiotics or immunosuppressive agents.

The oral carriage of *Candida* refers to the normal, symptom-free presence of *Candida* in the oral cavity without any clinically visible disease with a prevalence of 13% to 45% in healthy adults. Some studies have suggested that all patients who receive topical anti-inflammatory therapy should receive antifungal therapy to prevent oral candidiasis, regardless of their carrier status. However, if only a minority of the population are carriers, and if only carriers are susceptible to candidiasis, this would be inappropriate use of an anti-microbial agent.

The objectives of this retrospective study were to determine a) the prevalence of candidal carriage in a group of consecutive patients who were cultured for candida, including patients with inflammatory oral disease scheduled for treatment with topical immunosuppressive therapy and b) the incidence of oral candidiasis after initiation of steroid therapy. To fulfill these objectives, the medical records of patients who underwent pan-oral swab cultures for *Candida* between January 2009 and December 2013 were reviewed. Patients who were on steroid therapy and had at least one follow-up visit were included in the incidence study. Patients who presented with candidiasis or who were on an anti-fungal agent at the consultation visit were excluded.

Eighty-seven patients were evaluated for candidal carriage. Of these, 17 (20%) were candida-positive and 70 (80%) were candida-negative. Forty-five of the 87 patients were evaluated for the development of candidiasis after topical immunosuppressive therapy. Of these, 7 were candida-positive (16%) and 38 (84%) were not. There was no difference in the prevalence of carriage between the larger group and the smaller cohort ($p>0.5$).

Five of the 45 (11%) patients with follow-up developed candidiasis. Four of 7 (57%) patients who were candida-positive developed candidiasis while only 1 of 38 (3%) who were candida-negative did so. As such, candidal carriage is highly associated with the development of candidiasis ($p<0.0001$). Conversely, those without candidal carriage were unlikely to develop candidiasis. Because the prevalence of positive candidal carriage status is 16-20%, and candidiasis develops primarily in those with positive carriage, we suggest that it is inappropriate to provide prophylactic anti-fungal agents to all patients starting topical steroid therapy for management of oral inflammatory mucosal disease.

**Identification of prognostic factors following resection of colorectal liver metastases
in the modern era of treatment**

Cynthia L. Miller

Harvard Medical School, William Bosworth Castle Society, Class of 2017

Cristina R. Ferrone, MD

**Department of General Surgery, Division of General and Gastrointestinal Surgery
Massachusetts General Hospital**

Advanced surgical techniques and new effective chemotherapeutic regimens have increased resection eligibility for colorectal liver metastases (CRLM), warranting reevaluation of traditional prognostic factors. We sought to identify factors associated with overall (OS) and recurrence-free survival (RFS) in patients who underwent liver resection for CRLM in the modern era of treatment.

We identified 270 patients who underwent 292 curative liver resections for CRLM at our institution between 4/2000- 4/2014. All patients underwent resection of a primary colorectal cancer (CRC), and received contemporary systemic therapy with either Irinotecan and/or Oxaliplatin and 5-FU (FOLFOX, FOLFIRI). Clinicopathologic and treatment-related variables were evaluated for association with OS and RFS by multivariate analysis.

The majority of patients were male (54%) with a median age at liver resection of 60 years (29-83). Median size of the largest metastasis was 25mm (1-150mm). Synchronous lesions were common (63%) and 40% had bilobar metastases. Most patients (79%) received neoadjuvant chemotherapy prior to liver resection. A Clavien complication with score ≥ 3 occurred in 53 patients (19%). 90-day mortality rate was 2% (6/270). Actuarial 5-year RFS and OS were 24% (95% CI: 19-30) and 48% (95% CI: 40-55) respectively. Significant prognostic factors for poor RFS were lymphovascular invasion (LVI) in the primary colorectal cancer (CRC) ($p=0.001$) and higher pre- liver resection CEA ($p=0.003$). Prognostic factors for poor OS were venous invasion in the primary CRC ($p=0.024$), size of the largest metastasis ($p=0.021$), and higher Clavien score ($p=0.046$). Chemotherapy after liver resection was significant for improved OS ($p<0.001$). Margin status, primary N stage, number and distribution of metastases were not significant ($p>0.05$).

In the era of FOLFOX and FOLFIRI, good surgical outcomes with low complication rates allowing for post-hepatectomy chemotherapy significantly improve OS. Pathologic factors representing the biology of the disease including LVI and venous invasion in the primary, size of the metastasis, and CEA level negatively affect OS.

Lymphoma in Botswana: Demographics, Treatment, and Outcomes**Michael Milligan****Harvard Medical School, Francis Weld Peabody Society, Class of 2017****Scott L. Dryden-Peterson, MD****Instructor in Medicine, Infectious Diseases****Brigham and Women's Hospital**

In sub-Saharan Africa, there is mounting evidence of an emerging “second epidemic” of cancer among patients infected with HIV. The high prevalence of HIV, associated immune suppression, and limited medical resources across the region have resulted in increased rates of many cancers. In developed nations, introduction of HAART led to a decrease in the incidence of many AIDS-defining cancers including Non-Hodgkin's Lymphoma (NHL). Despite administering an expansive HAART program, the incidence of NHL has more than doubled in the sub-Saharan African nation of Botswana over the past decade. In order to improve care, this prospective cohort study sought to characterize the HIV status, demographics, treatment patterns, and outcomes of patients with NHL in Botswana.

The study enrolled patients 18 years or older, diagnosed with NHL between October 2010 and July 2014 at two major hospitals in Botswana. Baseline and quarterly follow-up information including the demographics, risk-factors, exposures, and clinical course of each participant was stored in an electronic database and analyzed using SAS 9.3. The primary outcome of the study compared survival time between HIV-positive and HIV-negative NHL patients, and was assessed using Cox-regression analysis.

In total, 52 patients met the selection criteria and were followed over a total of 53.1 person-years. Seventy-three percent of patients were confirmed to be seropositive for HIV within 1 month of cancer diagnosis, and were more likely to be female, younger, and more educated than their HIV-negative counterparts. Thirty-one percent of all patients faced delays longer than 6 months in receiving a cancer diagnosis after their initial presentation. Delays were most commonly associated with nonspecific presenting symptoms, challenges with pathological analysis, and limited access to physicians. All patients diagnosed with NHL were started on a chemotherapy regimen consisting of 8 cycles of either CHOP or R-CHOP. A minority of patients received regimen modifications due to clinical complications or drug supply issues. The mean survival time of all NHL patients was 13.5 months, with non-significant reductions in survival time associated with older age and advanced stage. There was an insignificant difference in the survival times of HIV-positive and HIV-negative patients.

These results indicate that despite limited medical resources and complications associated with HIV, seropositive patients with NHL tend to do as well as their seronegative counterparts. With its leadership position in combating HIV/AIDS, we believe that the experiences in Botswana will guide the understanding and treatment of NHL and other HIV-associated malignancies across sub-Saharan Africa.

Assessing Access to Subspecialty Care in Rural El Salvador**Andreas Mitchell****Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017****Jennifer Kasper, MD, MPH****Department of Pediatrics, Division of Global Health****Massachusetts General Hospital for Children**

Rural populations in El Salvador face barriers to subspecialty healthcare that lead to adverse health outcomes. In Estancia, El Salvador, the Centro de Integración de Atención, Prevención y Educación en Salud (“Center for Integration of Care, Prevention and Education in Health” or CAIPES) clinic has implemented a Subspecialty Referral Program to address barriers to high-quality, coordinated care. This study evaluated the needs of patients accessing the clinic and the efficacy of the Subspecialty Referral Program in meeting those needs.

This project was designed: (1) to characterize the subspecialty healthcare needs of patients accessing the CAIPES clinic, and (2) to assess the experiences and perceived health outcomes of patients utilizing the Subspecialty Referral Program.

CAIPES maintains an electronic database of subspecialty referrals, documenting patient demographics, reasons for the referral, and number of referrals per patient. We conducted a retrospective database review to characterize the patients benefiting from the referral program. Additionally, we conducted 47 interviews to identify patients’ perspectives on their experiences in the program. We sampled 20 patients with chronic conditions (defined as 5 or more referrals), 20 patients with non-chronic conditions, and 7 patients who benefitted specifically from the eye care fund. Interviews were conducted in patients’ homes with a community health worker serving as a cultural broker.

The database review revealed that the majority of funds go towards transportation and medications. Over the past five years, annual expenditures through the fund have been decreasing. The median amount of financial support was 18 USD per patient, and 87% of beneficiaries received \$100 or less. Future data analysis will integrate these data with the results of the interviews.

Preliminary results suggest that the referral program has saved several patients’ lives and improved quality of life for many others. Some patients reported issues with follow-up that led to diminished outcomes. Increased communication and coordination between the clinic and community health workers could augment the efficacy of this program. The relatively small quantities spent per patient suggest that this program could be replicated in other low-resource settings.

Incomplete data in the electronic database impeded certain calculations. However, to the best of our knowledge, we only derived the data reported from complete and accurate components of the dataset. There may also be limited generalizability, as the unique strengths and constraints of the community in Estancia may not translate to other locations.

**How Indigenous Guatemalan Women
Perceive and Interact with Non-governmental Organizations**

Jillian Moore
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Peter Rohloff MD, PhD
Department of Medicine
Brigham and Women's Hospital

Guatemala has one of the most disparate income distributions in the world, and the indigenous Mayan population is disproportionately impoverished compared to the general population. With the implementation of neoliberal policies intended to privatize, liberalize, and deregulate the economy, the Guatemalan state has abandoned many of its former social roles, and non-governmental organizations providing these social services have proliferated. Although many non-governmental organizations are well intentioned and possess valuable resources, we understand less about how they impact individual communities and aid recipients. Here we present an ethnographic study of how women in one rural indigenous Mayan town have experienced their interactions with non-governmental organizations, supplemented by structured surveys of how women in this town care of their families and acquire resources. We explore how the aid relationship intersects with other expectations and disparities these women face, how non-governmental organizations establish and maintain power in this relationship, and how women navigate the development sector in their town. This work may be useful to those who seek to better understand how to implement evidence-based development programs in local worlds, especially in communities that speak indigenous and minority languages, some of the most marginalized in the world.

BDNF and COMT polymorphisms mediate DLPFC-seeded connectivity during working memory

Alexander M Moscicki

Harvard Medical School, Walter Bradford Cannon Society, Class of 2017

Heike Tost MD PhD

Andreas Myer-Lindenberg MD PhD

**Systems Neuroscience Psychiatry, Department of Psychiatry and Psychotherapy
Central Institute of Mental Health, University of Heidelberg, Medical Faculty
Mannheim, Mannheim, Germany**

Disrupted prefrontal-hippocampal functional connectivity estimated from functional magnetic resonance imaging (fMRI) data is a well-established neural aberration implicated in schizophrenia. In particular, this abnormality manifests as a failure to reduce connectivity between the dorsolateral prefrontal cortex (DLPFC) and the hippocampus during working memory tasks.

Repetitive transcranial magnetic stimulation (rTMS) is technique that induces neuroplasticity via electromagnetic stimulation of cortical neurons. Application of rTMS to the DLPFC enhances reductions in DLPFC-hippocampal connectivity during working memory in healthy volunteers, suggesting the involvement of neuroplastic processes in this response. Indirectly, it implies a relation between abnormalities in DLPFC-hippocampal connectivity and well-known impairments in neuroplasticity associated with schizophrenia.

To investigate this implication, we tested whether three different genetic polymorphisms implicated in schizophrenia and neuroplasticity (COMT Val158Met, BDNF rs56164415, and CACNA1C rs1006737) alter DLPFC-seeded connectivity and its response to rTMS. In particular, we examined the individual and epistatic effects of these polymorphisms on sham-rTMS and rTMS DLPFC-seeded connectivity during a working memory task, using fMRI data acquired from 106 healthy volunteers.

There was a significant association between BDNF genotype and DLPFC-hippocampal connectivity, with Met allele homozygotes showing increased DLPFC-hippocampal connectivity compared to Val carriers. Similarly, Met homozygotes showed greater reductions in DLPFC-hippocampal connectivity following TMS stimulation than did Val carriers. Moreover, COMT and BDNF showed a significant epistatic effect on DLPFC-seeded connectivity in the left frontal superior medial cortex, which was embedded in a default mode like network that showed marginally significant COMT x BDNF epistasis.

These findings suggest that BDNF mediates DLPFC-hippocampal connectivity during working memory and that rTMS stimulation to the DLPFC normalizes increased DLPFC-hippocampal connectivity in BDNF Met homozygotes. Interactions between BDNF and COMT might also mediate connectivity between DLPFC and the default mode network during working memory. Collectively, these findings contribute to an evolving understanding of how genetic polymorphisms shape neural abnormalities associated with schizophrenia, providing insight into what Andreas Meyer-Lindenberg has termed, “neurogenetic mechanisms of risk” for the disorder. Given the availability of genetic and fMRI data in a group of over 600 healthy volunteers, we hope to replicate the findings on DLPFC-seeded connectivity in this larger sample.

**Estimating the Net Savings of A Comprehensive Population Health Management
Strategy At Partners HealthCare**

Andy Nguyen

Harvard Medical School, Francis Peabody Weld Society, Class of 2017

**Timothy G Ferris, MD, MPhil, MPH
Population Health Management
Partners HealthCare**

The rising cost of health care remains one of the most pressing challenges facing Americans. Despite sweeping health care insurance reforms at both the state and national levels within the last decade, reform efforts have focused most heavily on access, rather than cost. Partners HealthCare (Partners) based in Boston, MA has been involved in a multi-party transformation in payment models that could yield considerable return on investment while improving patient care and addressing systems-level health care spending growth.

Starting with a 2006 Medicare shared-risk demonstration project among medically complex, high cost patients, Partners began developing tactics to lower cost and improve outcomes in population health. This approach, called population health management (PHM), relied on data, measurement, and evidence-based methods of improving access, continuity, and care coordination. Positive results with PHM contributed to Partners' continued trial of a relatively novel payment modality, shared-risk contracts, and further developing a suite of PHM programs.

To evaluate the financial impact of implementing ten PHM programs across various care settings in the Partners system, we developed a model for each program estimating program costs and total medical expense (TME) reductions. Internal data were used to quantify target population sizes and costs of care within the Partners system. We extracted data from patient claims and hospital administration finances in aggregate, stripped of personal identifiers. A three-year projection (2015 to 2017) was estimated for each program, inclusive of assumptions regarding ramp-up to a 2017 program steady state. Target population sizes for each program were derived from demographic and aggregated health data about the Partners primary care patient population.

Cumulative net savings were defined as the difference between TME reductions and program costs for all programs modeled. Over a three-year period (2015-2017), our model predicted a cumulative net savings of \$290 million due to the suite of PHM programs. Program net savings were greatest in Year 3, at a sum of \$141 million. At Year 3, three programs—Mental Health Integration, Patient Centered Medical Home, and Integrated Care Management—yielded both the greatest TME reductions and cost savings.

PHM is one approach being tested in the field to reign in health care spending. Although this analysis presented positive savings due to PHM programming, these savings also came with a considerable amount of investment capital in the form of program costs. Given our predictions, the PHM framework may be of utility to planners and other care delivery systems.

Disparities in utilization of educational services for children with autism spectrum disorder

Cameron S Olezene

Harvard Medical School, William Bosworth Castle Society, Class of 2017

James Perrin, MD

Mass General Center for Child and Adolescent Health Policy

Massachusetts General Hospital

Objective: Our goal was to determine if there were any socioeconomic disparities in utilization of therapy, Individualized Family Service Plans (IFSPs) or Individualized Education Programs (IEPs) for children with autism spectrum disorder (ASD) and to see if parents' communication and interactions with providers influenced use of these services.

Methods: We used the 2011-2012 National Survey of Children's Health to identify 1,624 children with parent-reported current diagnosis of ASD. We used multivariate regression analyses to determine the impact of income and experience with providers on the use of therapy and IFSPs/IEPs. We controlled for race, parent education level and type of health insurance.

Results: Low income households were much less likely to report having received an IFSP/IEP during early childhood or having ever received therapy. Also, parents with children currently receiving therapy reported less satisfaction with communication among their providers and a need for more help with care coordination. Lastly, greater disease severity and knowing more than one provider well were found to be positively associated with receipt of therapy and IFSP/IEPs.

Conclusion: Significant economic disparities are present in the use of educational services for children with autism spectrum disorder. Additionally, parents accessing these services desire greater assistance with care coordination and greater communication among their providers. Greater communication and care coordination from providers could potentially be a mechanism for increasing the use of educational services for children with ASD, particularly for low income families who would stand to benefit most.

Palliative care issues encountered by radiation oncologists caring for advanced cancer patients

Gregory M. Parker

**Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017
Miliotis Fellowship in Pediatric Oncology**

Tracy A. Balboni, MD, MPH

**Department of Radiation Oncology
Brigham and Women's Hospital**

Palliative radiation therapy (PRT) is often administered to patients with advanced cancers. Among patients with metastatic cancer, 30 percent receive radiation therapy in their last year of life, and of those receiving radiation therapy in the final month of life 18 percent spent 10 or more of their last 30 days receiving radiation treatments. Despite frequently encountering patients who are in the last year or months of their life, the field of radiation oncology has had little academic emphasis on palliative care, including a paucity of education and research in this area. It is likely that patients present to radiation oncology clinicians with many palliative care needs requiring management. To date, the types and frequencies of palliative care issues encountered in this setting have not been characterized.

This study aims to assess the frequency and relevance of palliative care issues encountered by radiation oncology clinicians during PRT consults. This prospective, survey-based study assesses consecutive consults for PRT from 5/19/14 to 9/26/14 at three Boston-area, community and academic, hospital-based centers. Participating physicians and nurse practitioners complete a survey to identify and rank the relevance (5-point scale, 'not at all' to 'extremely') of palliative care issues. Eight domains adapted from national palliative care guidelines – physical symptoms, psychosocial issues, cultural considerations, spiritual needs, care coordination, advance care planning, goals of care, and ethical and legal issues – are evaluated. Preliminary descriptive statistics based on 93 completed surveys are reported (response rate = 93%; anticipated sample size = 198).

Most (82%) consults had 2 or more palliative care domains ranked as very or extremely relevant to patient care. The domains of physical symptoms (91%), care coordination (69%), and goals of care (53%) were very or extremely relevant in >50% of consults. Within these domains, the issues most often reported as relevant were interdisciplinary care coordination (90%), consideration of prognosis in treatment plan development (87%), pain management (72%), and discussion of patient values and priorities in treatment plan development (66%). Advanced care planning (24%), cultural considerations (9%), spiritual needs (9%), and ethical and legal issues (9%) were least commonly ranked as very or extremely relevant.

Radiation oncology clinicians encounter multiple palliative care issues when consulting on patients for PRT. Clinicians identified physical symptoms, care coordination, and goals of care as the most relevant palliative care domains. These findings can help guide palliative care development within radiation oncology, including education and structures of care delivery.

Exploring the effect of stroma-derived hepatocyte growth factor in breast cancer progression

Sachin Patel

Harvard Medical School, Walter Bradford Cannon Society, Class of 2017

**Robert Weinberg, PhD
Department of Biology, MIT
Whitehead Institute**

One of the major challenges in cancer therapy is drug resistance. Owing to the heterogeneity of most cancers, not all cells can be uniformly eradicated. Drug-resistant cells, though they may have been initially present at a low frequency, grow, divide, and eventually predominate. As a result of this selective process, they tend to be more aggressive, more difficult to kill, and usually signify a worse prognosis. Understanding how the heterogeneity of cancers is developed and maintained, thus, is critical to discovering new ways to overcome drug resistance.

This maintenance is in part due to the reactive stroma within which most tumors reside. Non-cancerous cells that constitute the tumor microenvironment, including fibroblasts, monocytes, pericytes, endothelial cells, and various immune cells, interact with cancer cells to drive tumor growth and survival. One specific factor that is secreted by fibroblasts is HGF, which is known to be present at high concentrations in the serum of cancer patients. In the context of normal development, HGF plays an important role in embryogenesis, wound healing, and organ regeneration. In dysregulated cancer environments, however, HGF enhances cell motility, local invasion, and proliferation in a manner distinct to that of other growth factors. This project seeks to examine how breast carcinoma subpopulations differentially interpret the HGF signal, with the hope of better understanding the mechanisms underlying tumor homeostasis.

We show that cell state, defined here as the degree to which a cell is differentiated, determines how breast carcinoma cells respond to HGF. Cells that have undergone an epithelial-mesenchymal transition (EMT) (mesenchymal-like) respond differently to HGF than do non-EMT (epithelial-like) cells. Epithelial-like breast carcinoma cells acquire a migratory phenotype when activated by HGF, whereas mesenchymal-like carcinoma cells instead proliferate when activated.

We further show that the migratory phenotype is dependent upon HGF-mediated upregulation of FRA1, a transcription factor downstream of the MEK/ERK pathway that has been implicated in cell motility, invasion, and survival programs. Preliminary work also suggests that HGF dependent increases in c-MYC and cyclin D1 may explain the mechanism through which HGF induces proliferation in mesenchymal-like cells.

Tissue Engineered Bone with Three-Dimensionally Printed β -TCP/PCL Scaffolds and Early Implantation: An *in vivo* Study in a Porcine Mandible Model

Adam Patenaude

Harvard School of Dental Medicine, William Bosworth Castle Society, Class of 2017

Maria Troulis DDS, MSc

**Department of Oral and Maxillofacial Surgery
Massachusetts General Hospital**

Bone penetration depth and angiogenesis is a current challenge in tissue engineering. This study looked to evaluate these challenges using 3Dimensionally (3D) printed β -Tricalcium phosphate (β TCP) /Polycaprolactone (PCL) scaffolds, seeded with pBMPC, incubated *in vitro* for 2 weeks. The scaffolds were then implanted into critical size mandibular defects within a porcine model for reconstruction.

This study was proof of concept to show bone formation in a critically sized gap could be achieved with β TCP and PCL scaffold and support angiogenesis. The second aim was to show that a 3-D printed material with controlled parameters could be used to enhance production and lower cost in future tissue engineering endeavors.

Using 50% β TCP and 50% PCL the scaffolds were 3D printed. Porcine bone marrow derived progenitor cell harvesting, isolation, expansion and differentiation into osteoblasts was performed so they could be seeded into the scaffolds. Construct incubation in a rotational oxygen-permeable bioreactor system for 14 days followed. Twelve critical size defects were created in two minipigs, six per mandible. Within the defects there were six experimental constructs placed as well as six controls consisting of three scaffolds and three empty defects. 56 days after the operation, the 12 defects were harvested. A combination of H&E staining and DAPI staining was used to analyze the slides. Cellular penetration depth and the amount of bone formation was determined using slides representing the centers of the defects.

Peripheral bone formation is indistinguishable from native bone in all 12 specimens. Four of the six constructs showed bone formation in the center of the repaired defect. A significant difference between the scaffold and construct bone formation was observed using histomorphometric analysis ($P < 0.05$), with 2.6% and 23.8% bone formation respectively. Although bone formation wasn't present, cell penetration depth was evident with 2109 cells/57mm² in the center of the two constructs compared to 1114 cellules/57mm² in the controls ($p < 0.05$).

3D printed β -TCP/PCL scaffolds, seeded with pBMPC show promise for tissue engineering of bone. When early implanted in a porcine critical size mandibular defect bone and cellular penetration are observed. Before a clinical application can be considered larger sample sizes and future study would be required.

**Timing the Delivery of Placenta Accreta with Placenta Previa:
The Decision to Deliver at 34 Weeks or Later**

Nicola Perlman

Harvard Medical School, Walter Bradford Cannon Society, Class of 2017

Daniela Carusi, MD, MSc

Obstetrics and Gynecology, Brigham and Women's Hospital

Placenta accreta, a condition of morbidly adherent placenta, has been increasing in incidence in the last few decades, now occurring in about 1/533 pregnancies in the United States. A significant risk factor for placenta accreta is placenta previa. A concurrent diagnosis of these conditions requires antenatal considerations and careful planning of delivery in order to prevent significant maternal and fetal morbidity. Discrepancies in opinion currently exist as to whether the least overall morbidity occurs with a delivery in the 34th week of gestation or after.

To determine optimal delivery timing for women presenting with radiologic diagnoses of previa and suspected accreta, we retrospectively followed a cohort of patients between 1997 and 2013 receiving care at Brigham and Women's Hospital (BWH). After determining what percentage of women in our cohort had deliveries within the 34th week of gestation versus the 35th week and later, the morbidity of the two groups could then be compared.

A preliminary data review of our cohort showed 9 deliveries scheduled during the 34th week of gestation (group 1) and 73 deliveries that were unscheduled or scheduled after the 35th week of gestation (group 2) with a median of 36.3 weeks gestation (34.0-38.9). All deliveries were via cesarean. The median estimated blood loss for group 1 was 3000 mL versus 1500 for group 2, while 78% of group 1 received a transfusion compared to 44% of group 2. Further, 11% of subjects with scheduled deliveries in the 34th week were admitted to the ICU as opposed to 8% of those scheduled later. Because of standard of care for infants delivered before 35 weeks gestation, 100% of the neonates born to group 1 were admitted to the NICU, versus 39% in group 2. Sixty-seven percent of our total cohort had placenta accreta confirmed pathologically, while 22% had no accreta confirmed either clinically or pathologically.

These preliminary results suggest that delivery of suspected accreta patients after 34 weeks does not significantly increase morbidity for pregnant women and probably decreases morbidity for infants. However, the patients delivered at 34 weeks may have been at higher a priori risk for morbidity, and these results do not take into account confounding variables. We plan to further review the results to determine whether or not significant morbidities prior to delivery increased the risk of adverse outcomes. We hope to use our data to inform future care and management of patients with placenta previa and accreta.

Evaluation of a School-based Mental Health Intervention in Haiti**Rachel Perron Wood****Harvard Medical School, William Bosworth Castle Society, Class of 2017****Anne E. Becker, MD, PhD, SM****Department of Global Health and Social Medicine, Harvard Medical School****Department of Psychiatry, Massachusetts General Hospital**

In Haiti the combination of an earthquake and cholera epidemic have exacerbated an urgent need for mental health services. Training teachers to assist students to navigate available mental health care may be a way to leverage scarce health resources and expand access to care for youth in need.

Study aims were to: (1) Assess feasibility, acceptability, and effectiveness of a school-based teacher accompagnateur program in Haiti. (2) Evaluate the relationship between students' past health care access/level of need and successful program engagement.

Secondary school teachers (n=22) in Haiti participated in a three-day training and were then matched with students (n=120) for mental health accompaniment. Students completed baseline self-report and interview-based psychosocial evaluations. They underwent additional clinician evaluations and received recommendations and referrals as indicated. Student-teacher pairs were encouraged to meet as a means of supporting access to mental health care; meetings covered school performance, wellness, and/or adherence to clinical recommendations. After the study, students completed a Likert-style questionnaire giving feedback on the program. Feasibility, effectiveness, and acceptability were operationalized from this questionnaire. We used multivariable regression models to examine predictors of program feasibility and effectiveness.

Only 52.5% of students had accessed general medical care in the past 12 months and only 12.5% had accessed mental health care in this time. Despite low previous access, a majority (73%) of students received a referral during the clinical interview. Prior access did not predict need for referral.

Feasibility—A large proportion (68%) of students met with a teacher. Perceived meeting feasibility and willingness to discuss treatment significantly predicted successfully completing a meeting (p values all <0.05).

Effectiveness—Significant predictors of effectiveness were: meeting with the teacher, willingness to discuss treatment, and finding the clinical team to be available as needed.

Acceptability—Significantly predicted by learning from the teacher or finding clinical recommendations useful.

There is a high level of need for improved access to mental health care among this sample of youth in Haiti, as evidenced by poor previous access to care and a high percentage of student participants being identified as needing a mental health referral. This teacher-accompagnateur program was feasible, acceptable, and effective. This program was successful for students regardless of previous ability to access care, suggesting that it is a plausible way to help a wide range of students navigate available resources.

Pharmacologic Modulation of Tumor Associated Macrophages**Alexandra Pourzia****Harvard Medical School, Francis Weld Peabody Society, Class of 2017****Anthony Letai, MD, PhD****Department of Hematologic Neoplasia/Malignancies
Dana-Farber Cancer Institute**

Macrophages within tumors, known as tumor-associated macrophages, can account for up to half of tumor mass. Tumor-associated macrophages are polarized towards the M2 phenotype, and secrete factors that assist with angiogenesis, tumor growth, metastasis, and local immunosuppression. In contrast, M1 macrophages exert anti-tumor effects. Activating tumor-associated macrophages towards the M1 phenotype is a potential therapeutic strategy.

Prior data from the Letai lab demonstrated that a novel compound, X, decreased tumor growth in a mouse model of breast cancer. The Letai lab also previously demonstrated that M1 macrophage-conditioned media increases breast cancer cell apoptotic “priming”, or readiness to undergo apoptosis. We hypothesized that compound X decreased tumor growth by modulating tumor-associated macrophages towards an M1 phenotype.

In order to test this hypothesis, RAW254.7 murine macrophages were cultured with the human breast cancer cell line MCF7 in the presence of M1-polarizing factors (LPS and IFN γ), DMSO control, or compound X. The MCF7 cells were collected for BH3 profiling, an assay developed by the Letai lab to measure how “primed” cells are to undergo apoptosis. We did not observe significant increases in priming in MCF7s cultured with macrophages receiving compound X, whereas macrophages treated with LPS and IFN γ did increase MCF7 cell priming.

Additionally, a luciferase reporter system was utilized to assess NF- κ B activity. RAW254.7 cells were treated with IFN γ and LPS, DMSO control, or increasing doses of compound X. While IFN γ and LPS stimulation induced a strong reporter signal at 8 hours, no similar signal was observed upon treatment with compound X, even at 24 hours.

To query another readout of M1-polarization, ELISA assays for M1-secreted cytokines (Tnf α and IFN γ) were performed. RAW254.7 cells were treated with LPS, DMSO, and compound X. We observed that while LPS was capable of inducing cytokine secretion, compound X did not induce either IFN γ or TNF α secretion compared to DMSO-treated cells.

These results indicate that compound X may cause macrophages to lose M2 characteristics, instead of modulating them towards the M1 phenotype. Future experiments will determine whether readouts of M2 polarization are decreased in macrophages treated with compound X. However, these results do not rule out the possibility that compound X is able to modulate macrophages towards the M1 phenotype. The RAW254.7 cell line may respond differently to compound X than macrophages in the murine model; or compound X may alter M1 markers that were not assessed. These possibilities will be explored in future studies.

Establishing a Relationship Between Home Literacy Environment and Brain Activity in Pre-reading Children

Sara J. Powers

Harvard Medical School, Walter Bradford Cannon Society, Class of 2017

Nadine Gaab, PhD

**Laboratories of Cognitive Neuroscience, Division of Developmental Medicine
Boston Children's Hospital**

To better understand the role of the environment in cognitive and language development, an increasing number of studies have examined how socioeconomic status (SES) affects underlying neural mechanisms of cognition and language in children. Results from these studies reveal correlations between SES and both brain structure and function during language tasks.

SES, however, only reflects certain characteristics of a child's background. The home literacy environment (HLE), characterized by the literacy-related interactions and resources in the home, experienced by children from infancy throughout the preschool years may modulate language development independently of SES. In behavioral studies, HLE has been shown to account for much of the observed effects of SES on language and cognitive performance. Importantly, increased brain function during language tasks previously associated with high SES may instead reflect an independent effect of HLE.

This study aimed to identify the relationship between HLE and brain activity in children during a language task. We hypothesized that subjects with higher HLE would demonstrate increased activation in language-associated regions when controlling for SES. We gathered fMRI data from pre-reading subjects (n=50) during a phonological processing (the ability to manipulate the sounds of language) task and correlated functional data with a composite HLE score while controlling for phonological skill and parental education, a measure of SES. Subjects also completed a behavioral testing session to characterize their language and pre-reading skills. HLE and parental education were determined using parental questionnaire responses.

Whole-brain multiple regression analysis revealed correlations between HLE and brain activity in several cortical regions previously related to language function, including bilateral fusiform gyri, left inferior frontal gyrus and right superior temporal gyrus ($p < 0.001$, uncorrected, minimum cluster size of 15 voxels). Parental education and HLE were not correlated ($P > 0.05$) which is likely the result of the high SES backgrounds of our cohort. Behavioral scores fell within average ranges, except for verbal IQ, which was significantly higher in our sample.

These data indicate that activation in several language-supporting brain regions is positively associated with HLE, demonstrating a relationship between HLE and brain function for the first time. Due to the homogenous socioeconomic backgrounds of our subjects, future work will need to incorporate subjects with more diverse HLE. This knowledge will broaden our understanding of how the environment shapes language development in order to provide children the greatest opportunity for success in reading.

A comparative biomechanical study of the surgical reconstruction of the scapholunate interosseous ligament

Prashant V. Rajan

Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Charles S. Day, MD, MBA

**Upper Hand & Extremity Surgery, Department of Orthopedics
Beth Israel Deaconess Medical Center**

The scapholunate interosseous ligament (SLIL) is located between the scaphoid and lunate bones of the wrist. SLIL injuries typically occur due to a fall on an outstretched hand and present as partial or complete tears. Complete tears of the SLIL may or may not present with static widening of the scapholunate interval in the coronal plane (contingent upon injury to additional scapholunate ligamentous stabilizers) and rotary subluxation of the scaphoid in the sagittal plane. If left untreated, these abnormal wrist kinetics can progress to degenerative arthrosis of the radioscapholunate joint.

In chronic SLIL injuries, the ligament remnants have degenerated and are no longer available for primary repair. In these situations, a reconstructive method is needed that corrects the abnormal scaphoid kinetics and reduces the scapholunate gap, if one is present. However, the surgical course of action here is controversial. Some studies have approached these injuries with a dorsal capsulodesis technique that utilizes a soft tissue slip from the dorsal wrist capsule or the dorsal intercarpal ligament to stabilize the distal pole of the scaphoid. Others have utilized a triligament tenodesis procedure that utilizes a flexor carpi radialis autograft to anchor the dorsal scaphoid to the dorsal radius. Both of these techniques solely focus on reconstructing the dorsal SLIL, which has the greatest contribution to ligamentous tensile strength (260 N). However, biomechanical evidence has also demonstrated the importance of the volar aspect (115 N) to the strength of the SLIL. Based on these findings, we hypothesized that a surgical front-back looping technique that utilizes a palmaris longus autograft to reconstruct both dorsal and volar aspects of the SLIL will provide better functional biomechanics.

To test this hypothesis, $n = 20$ cadaveric wrists were dissected to expose and section the SLIL and 5 wrists each were reconstructed using one of three surgical techniques: dorsal capsulodesis, triligament tenodesis, or front-back looping. The remaining 5 wrists were assigned to a control group where the SLIL was exposed and kept intact. The wrists are currently being subjected to motion simulation analysis where intercarpal joint pressures, biomechanical range of motion, scapholunate displacement, and graft load to failure data will be gathered and compared. We expect that incorporation of the volar SLIL in the reconstructive technique will provide statistically improved range of motion, smaller scapholunate displacements, a higher load to failure, and a pressure profile that is similar to the control wrists.

An Analysis of Healthcare Spending Broken Down By Clinical Episodes**Chanan Reitblat****Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017****Michael E. Chernew, PhD****Department of Healthcare Policy****Harvard Medical School****Zach Cooper, PhD****Assistant Professor of Public Health****Yale School of Public Health**

Policy makers and private stakeholders need better information on sources of spending increases to support a range of policy initiatives. Current measures of spending growth are generally organized by site of care (physician office, hospital, drug) or the patient. This measurement orientation contributes to the fragmented nature of our payment and delivery systems and impedes a transition towards patient-centered care. New payment models (such as bundled payments in Medicare or with the state initiative in Arkansas) are clinically oriented but information for updating payment is lacking. Existing payment models (e.g., Inpatient PPS or RBRVS) typically rely on a conversion factor that, when updated, affects all services equally. Yet because broader payment bundles are subject to different rates of technical change, uniform updating may be particularly inappropriate for bundled payment systems. Moreover, an episode perspective will allow policy makers to better assess the role of technical change (and its appropriateness) vs. price or other factors in driving spending growth. Such analysis could provide insight about the causes, and maybe potential persistence, of the spending slowdown. Episode based growth analysis may also help target clinical areas for attention. For example, a growth in imaging, hospital days, or prescriptions may or may not be appropriate, depending on the clinical condition. Interpretation of growth in hospice may depend on which clinical conditions are accounting for such growth. Furthermore, effective payment policies also require a clear understanding of what contributes to wide geographic variation in spending levels across the country and differences in rates of growth for Medicare and private payers. To monitor trends and inform payment or other policies seeking to slow health care spending while preserving access, this project will use Medicare and private insurance claims data to develop a new dashboard to examine changes in total spending by episodes of care, constructed to enable decomposition by price and use components across a continuum of services. The dashboard and trend analyses will inform payment update and bundling policies as well as provide insight regarding the impact of technology on spending growth. The national and state level dashboard will consist of an enriched set of spending indicators and time trends to inform policy decisions.

Evaluating the prevalence and causes of anemia in females in India using needleless technology**Dodie Rimmelin****Harvard Medical School, William Bosworth Castle Society, Class of 2017****Nupur Gupta, MD****Division of Adolescent and Young Adult Medicine****Division of Global Health****Massachusetts General Hospital**

The burden of anemia in India is of huge public health significance. A large proportion of the population is affected and the deleterious effects of the disease are harming the health, development and economy of entire generations. Research and efforts to combat this epidemic have focused primarily on pregnant women and children under five years of age, and have failed to achieve significant improvements. The adolescent female population has been left out of national data collection efforts and interventions, despite adolescence being a particularly vulnerable period, as well as an opportune time for detection and correction of anemia.

We worked with females ages 10 to 25 in two states in India, Rajasthan and Maharashtra, in order to evaluate the prevalence of anemia using needleless technology. We sought to assess the feasibility of using the non-invasive Masimo Pronto-7 device as a novel diagnostic method with the potential to reduce discomfort and provide an accurate assessment of anemia in a resource-limited, rural setting. In addition, we aimed to determine factors contributing to high rates of anemia in these populations, as well as reasons interventions have not succeeded, despite longstanding efforts by the government.

In each state, we randomly selected villages from among those in which our Indian partners worked. Within the selected villages, we used cross-sectional, convenience sampling, recruiting participants at schools, village-level meetings and at the household level. We measured participants' hemoglobin, heights, and weights and administered questionnaires, which recorded information on diet, symptoms, recent illnesses, family history, menstrual and obstetric history, use of iron supplementation and knowledge on anemia. We enrolled a total of 428 participants—168 from Maharashtra and 260 from Rajasthan.

The majority (63.6%) of those we sampled had anemia. A third (32.4%) had mild anemia, 27.7% had moderate anemia, and 3.5% had severe anemia. We found low rates of knowledge on anemia, with 71.1% of participants having never heard of anemia and only 15.1% exhibiting some knowledge on its symptoms, causes or prevention. Amidst high levels of anemia in this population, only 16.8% were taking iron supplementation. The most common reasons for not taking supplementation were having not been offered, despite a national government program that distributes supplements in schools. The non-invasive Masimo device was found to be a relatively good tool in this setting and population; for 88.2% of those enrolled, we were able to get a hemoglobin reading on the first or second attempt.

Our study pointed to a huge need for education on the causes, prevention and treatment of anemia, as well as enhanced access to iron supplementation. In addition, it demonstrated the potential of non-invasive hemoglobin testing in a rural, global health setting.

Evaluation of a Malnutrition Intervention Program in Small, Rural Salvadoran Community**Rachael Rosales****Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017****Jennifer Kasper, MD, MPH****Department of Pediatrics, Division of Global Health
Massachusetts General Hospital for Children**

Worldwide, estimations cite malnutrition as a factor in 50-66% of all under 5 mortality. Even when it doesn't cause mortality, inadequate nutrition permanently impacts a child's growth and development. This research was conducted in La Estancia, a small, rural community with some of the worst health indicators in the country, with high rates of childhood undernutrition. Before the program was implemented, measurements in September 2013 indicated that 15% of children were acutely malnourished and 38% were chronically malnourished. Food costs increase so quickly that one-third of the people cannot afford basic foods. *La Asociación de Campesinos para el Desarrollo Humano* (Peasants for Human Development, CDH) is collaborating with the United Nations World Food Program (UN WFP) to reduce poor childhood nutrition in Estancia. The project includes nutrition education and distribution of nutritional supplements. The local community health workers give monthly talks about proper nutrition, especially for pregnant women and children, and they conduct anthropometric measurements every two months. During the months that measurements are taken, enrolled families receive corn, beans, and the Super Cereal *plus* (every two months).

The first objective was to support the collection and analysis of anthropometric data of children under the age of 2 to measure the prevalence of different forms of malnutrition. The second objective was to assess effectiveness of the program on reducing and preventing the prevalence of the different types of childhood malnutrition. The working hypothesis was that the program would decrease malnutrition but not eliminate it.

Work done included supporting community health workers as they made home visits, giving educational talks, and conducting bimonthly measurements of weight-for-age and height-for-age. The latest analyzed cross-sectional data shows that 12% of children are acutely malnourished and that 48% are chronically malnourished. More analysis is needed to understand the trends of individual children and different cohorts.

Overall, the program appears to help counter acute malnutrition, but chronic malnutrition continues to be a widespread and worsening problem. Further analysis will help to elucidate the program's impact. More longitudinal interventions and data are needed to conduct a more thorough and useful evaluation. Furthermore, a more integrated and multidisciplinary approach will be needed to address additional economic and agricultural factors that limit food security and nutrition. The conclusions of this research will be limited by the fact that CDH has not collected or stored much longitudinal data and also because child growth isn't the most sensitive marker.

**Effects of Mutant Calreticulin on Megakaryopoiesis in *JAK2*-unmutated
Myeloproliferative Neoplasms**

Emily A. Rosen

**Harvard Medical School, Irving M. London Society, Class of 2017
American Society of Hematology HONORS Award**

Ann Mullally, MD

**Division of Hematology
Brigham and Women's Hospital**

Somatic mutations in calreticulin (*CALR*) have been reported in the majority of *JAK2*-unmutated, *BCR-ABL*-negative myeloproliferative neoplasms (MPN). Approximately half of all essential thrombocythemia (ET) and primary myelofibrosis (PMF) cases are characterized by *CALR* mutations – the two most common are a 52-basepair deletion and a 5-basepair insertion in exon 9, leading to a novel C-terminus. However, the mechanism by which mutant *CALR* (m*CALR*) leads to clonal expansion of myeloid cells to induce MPN is not understood. Because megakaryocyte hyperplasia is a defining feature of ET and PMF, we focused on m*CALR*'s effects on megakaryopoiesis. Furthermore, we hypothesized that m*CALR* affects megakaryopoiesis by conferring cytokine hypersensitivity, leading to myeloproliferation.

To investigate the effects of m*CALR* on megakaryocyte differentiation, we over-expressed mutant or wildtype (wt) *CALR* in primary human CD34⁺ hematopoietic stem and progenitor cells (HSPCs) using a lenti-viral vector. After culturing the cells *in vitro* with stem cell factor (SCF) and thrombopoietin (TPO), megakaryocyte differentiation among cells expressing m*CALR* and wt*CALR* was compared by flow cytometry. We observed a higher percentage of megakaryocytes among cells expressing either of the two mutated forms of *CALR* compared to cells expressing wt*CALR* or empty vector.

To investigate the effects of m*CALR* on megakaryocyte polyploidization, we over-expressed mutant or wildtype (wt) *CALR* in primary murine HSPCs using a retroviral vector. After culturing the cells *in vitro* with SCF and TPO, we found that megakaryocytes over-expressing m*CALR* demonstrated increased polyploidization, evidenced by a higher percentage of 16n megakaryocytes, compared to megakaryocytes expressing wt*CALR* or empty vector. Since polyploidization indicates a more mature megakaryocyte, we speculate that m*CALR* may lead to accelerated polyploidization and terminal differentiation.

To study the effect of m*CALR* on cytokine sensitivity, we used IL-3-dependent murine hematopoietic Ba/F3 cells, over-expressing the TPO receptor, *MPL*. Under starvation conditions, Ba/F3-*MPL* cells expressing m*CALR* showed increased phosphorylation of the intracellular signaling molecules *STAT5* and *STAT1* compared to Ba/F3-*MPL* cells expressing wt*CALR* or empty vector. In this system, m*CALR* transforms Ba/F3-*MPL* cells to IL3-independence. We hypothesize that m*CALR*-expressing Ba/F3-*MPL* cells are hypersensitive to trace amounts of cytokine present under starvation conditions and accounts for the differential *STAT5* and *STAT1* activation we observed.

In aggregate, our data indicates that m*CALR* expression promotes megakaryocyte differentiation and polyploidization through cytokine hypersensitivity and activation of downstream *STAT* signaling proteins. This work provides insight into the mechanism by which mutant *CALR* expression causes MPN in patients who harbor *CALR* mutations.

Characterization of the role of the nucleus reuniens in prefrontal cortex and hippocampal synchronization

Alexis T. Roy

Harvard Medical School, Francis Weld Peabody Society, Class of 2017

Bernat Kocsis, MD, PhD

Psychiatry Department

Beth Israel Deaconess Medical Center

Cognitive dysfunction is a debilitating symptom of schizophrenia that largely results from impaired communication between the hippocampus and prefrontal cortex (PFC). Normally, the hippocampus and PFC generate oscillatory (rhythmic) electroencephalographic (EEG) activity, and synchronization of these oscillations can facilitate long-range communication between these structures. Specifically, synchronization of the PFC to theta (4-7 Hz) oscillations generated in the hippocampus may allow the PFC to make executive decisions based on memory. Deficits in generating theta synchronization may contribute to the pathophysiology of key clinical features of schizophrenia, including impaired decision-making and problem solving.

Although the hippocampus and PFC must communicate to accomplish a variety of complex tasks, the specific pathways by which this synchronization occurs are less clear. The hippocampus communicates to the PFC through not only a direct projection, but also indirectly through the reuniens—a nucleus in the thalamus that is thought to play a role in regulating informational flow based on arousal state. The aim of this project was to understand the pathway by which the PFC can synchronize with the hippocampus. We hypothesized that the reuniens plays a role in modulating communication from the hippocampus to the PFC, and that PFC synchronization to theta frequencies generated by hippocampus may involve this indirect pathway.

Experiments were performed in 10 rats under urethane anesthesia. Stainless steel recording electrodes were stereotactically implanted in the hippocampus, reuniens, and PFC. A stimulating electrode was implanted in the pontine reticular formation, a region of the brainstem that induces theta rhythm in the hippocampus upon excitation. This region was stimulated using 100 Hz square waves for 10 s at different intensities, while local field potentials were recorded. Brains were sliced, mounted, and stained with cresyl violet to confirm electrode placement. Peak theta frequencies and average power within the theta range during the stimulation period (relative to baseline) were calculated for 3 rats.

Theta frequencies and power increased in the hippocampus with increasing stimulation intensity. Theta oscillations in reuniens and PFC only appeared at high intensity stimulation such that theta power was greater and appeared earlier in reuniens than in PFC. This power pattern may indicate that the hippocampus is communicating to the PFC through the reuniens. In conclusions, these preliminary results provide evidence that the reuniens may play a role in mediating theta frequency synchronization between the hippocampus and PFC.

Vitamin D Metabolism in Pre-Pubertal Subjects**Brian L. Ruggiero****Harvard School of Dental Medicine, Oliver Wendel Holmes Society, Class of 2017****Julie Glowacki, PhD****Department of Orthopedic Surgery****Brigham and Women's Hospital**

Vitamin D is crucial in the maintenance of mineral homeostasis and the formation of new bone. A disruption of this homeostasis can lead to a pathologic state of low bone density including both rickets and osteoporosis. Vitamin D contributes to bone metabolism by inducing the differentiation of human marrow stromal cells (hMSCs) into osteoblasts, the bone forming cell. Vitamin D is converted from its inactive form, 25(OH)D, to its active form, 1,25(OH)₂D, by the enzyme CYP27B1 in renal tubular cells. It was recently discovered that this enzyme is expressed in the hMSCs, suggesting an autocrine/paracrine role of Vitamin D in bone metabolism. These cells showed an age related decline in both the expression and activity of the CYP27B1 in adult and elderly populations. 25(OH)D has also been shown to have effects on various proteins related to vitamin D metabolism including the vitamin D Receptor, the 25 and 24 hydroxylases and CYP27B1.

The biochemical environment of bone is known to be quite different in pediatric individuals compared to adults and elders and thus, we investigated the expression and activity of CYP27B1 in pre-pubertal individuals. We hypothesized that these subjects would show an increased level of expression and activity of CYP27B1 based on previous findings. hMSCs were isolated from 12 subjects (average age is 9.5 ±0.3 years) via centrifugation using ficoll histoplaque from discarded iliac crest bone marrow in patients needing a bone graft in the repair of an alveolar cleft. Cells were then grown in culture and all experiments were conducted at similar confluence and at the 2nd passage. To determine if pre-pubertal cells have the ability to biosynthesize 1,25(OH)₂D from 25(OH)D, cells were grown in 12-well plates and treated with or without 1uM 25(OH)D for 24 hrs. CYP27B1 activity was expressed as 1,25(OH)₂D concentration in the media measured via ELISA. The effect of 25(OH)D on gene expression was analyzed by treating cells in 100mm dishes with or without 10nM 25(OH)D for 24 hrs. RT-PCR was used to analyze gene expression for both the constitutive group and the experimental groups.

Constitutive expression of CYP27B1 was found to be higher in the male subjects than the female subjects (p=.04) however, there exists a statistically significant difference in age between male and female subjects (p=.01). Further statistical analyses will determine whether there is a true gender effect. All other data has been collected and will be analyzed in the upcoming weeks.

**Novel Mechanism of Atherosclerotic Plaque Rupture:
Zooming in on the Genesis of Microcalcifications**

Jessica L. Ruiz

Harvard Medical School, Irving M. London Society (HST), Class of 2017

Elena Aikawa, MD, PhD

**Department of Medicine, Cardiovascular
Brigham and Women's Hospital**

Atherosclerotic plaque rupture is responsible for over 50% of cardiovascular deaths in the U.S., due to the precipitation of fatally occlusive atherothrombosis. Finite element analyses have indicated that microcalcifications ($<5\ \mu\text{m}$) can amplify stress within the thin atherosclerotic fibrous cap and induce rupture. Matrix vesicles (MVs), known to drive early mineralization in bone, have been observed in association with calcium phosphate crystals in atherosclerotic lesions; however, the mechanisms by which MVs lead to microcalcification formation remain unknown. We hypothesize that MVs released within an atheromatous lesion aggregate in the fibrous cap, nucleating stress-inducing microcalcifications that increase the risk of cap rupture.

Two different collagen-based, three-dimensional, *in vitro* models of the fibrous cap were developed, each tailored to address specific questions. The initial stages of MV aggregation and mineralization were characterized with the first model, utilizing super-resolution microscopy techniques. Collagen hydrogels were cast as 8mm x 8mm x 2mm gels, incubated with fluorescently-labeled MVs, stained for hydroxyapatite, and fixed, mounted and imaged using structured illumination microscopy. Preliminary images have shown structures resembling confocal microscopy images of microcalcifications in sectioned human carotid artery, indicating that our *in vitro* system adequately recapitulates *in vivo* phenomena.

The second model was designed to quantify MV diffusion and aggregation. Collagen gels were cast in 1mL syringes, submerged in media containing fluorescently-labeled MVs, and incubated, allowing for MV diffusion into the gels. Once the system is finalized, the rate of diffusion will be quantified by sectioning the gels into 3mm disks, digesting and analyzing for changes in MV fluorescent intensity as a function of gel depth. The systems were optimized for ideal gel shape, handling and imaging. Further optimization studies are underway to maximize the signal-to-noise ratio of the fluorescent MV and hydroxyapatite labels, crucial for both imaging and diffusion analyses.

Ultimately, the aggregation model imaging will be used to analyze interactions between individual MVs and between MVs and collagen, and to capture the initial stages of mineralization. Further, the quantitative diffusion data will be used to develop a mathematical model of MV diffusion and aggregation in collagen gels of varying densities. Both of these models can also be used to characterize the efficacy of anti-calcific drugs. A better understanding of these processes will play a pivotal role in redefining the determination of atheroma vulnerability to rupture, and can reveal new therapeutic targets.

**Adaptation and Pilot of the Nutrition Environment Measurement Tool for Stores
(NEMS-S) in Central and Western Cuba**

Anna M. Ruman

Harvard Medical School, Walter Bradford Cannon Society, Class of 2017

Paul E. Farmer, MD, PhD

**Department of Global Health and Social Medicine, Harvard Medical School
Division of Global Health Equity, Brigham and Women's Hospital**

Cuba has experienced rapidly increasing obesity rates over the last fifteen years. Among other factors, consumer nutrition environments – defined by the availability, price, and quality of healthy foods – predict individuals' food choice and population-level obesity prevalence. However, data describing Cuba's nutrition environment remain scarce. Furthermore, existing assessment instruments, such as Glanz, et al.'s Nutrition Environment Measures Survey for Stores (NEMS-S), have not been validated in the Cuban context. Consequently, our project aimed to modify NEMS-S for use in Cuba and pilot the adapted instrument in urban, peri-urban, and rural Cuban communities.

We first modified NEMS-S to incorporate typical healthy and unhealthy Cuban foods; key informant interviews strongly influenced this process. Next, we utilized housing quality and population density data to identify two 1 km squared survey tracts, one each in the cities of Havana and Cienfuegos. Rather than pilot the adapted NEMS-S in peri-urban and rural Cuba, we deviated from our initial project plan; controlled for urban location, population density, and socioeconomic status; and varied by region to account for regional dietary variation. We piloted the adapted NEMS-S in a total of 39 food retail outlets (19 in Havana, 18 in Cienfuegos) classified into five distinct categories, collecting data on indicator food availability, price, and quality.

Our data analysis will include descriptive statistics for both composite and non-composite food availability, price, and quality for the 10 indicator food categories, five types of food retail outlets, and two regions. We will also utilize geomapping techniques to map distribution and type of food outlets within the two survey tracts to assess the viability of mapping community nutrition environments in limited resource settings. Lastly, we will leverage qualitative analysis techniques to assess how effectively the adapted NEMS-S captures: A) availability, price, and quality of typical healthy and unhealthy Cuban foods; and B) the uniqueness of Cuba's socialist food system and food pricing structure.

Project findings will impart improved understanding of factors influencing obesity prevalence in Cuba; suggest public health policy implications, both for Cuba and other countries; provide baseline data describing the Cuban nutrition environment before trade liberalization with the United States; and offer insight into how to best modify nutrition environment assessment instruments for developing country settings.

**3-dimensional Anthropometric Characterization of the Oral Region for the
Malaysian Malay Ethnic Group**

Laura E. Rushford

Harvard School of Dental Medicine, William Bosworth Castle Society, Class of 2017

David Ngeow, BDS, FFDRCS, FDSRCS, MDS, PhD

Department of Oro-Maxillofacial Surgical & Medical Sciences

University of Malaya

Anthropometry, the science of measuring the human body, has been widely used in the healthcare profession to establish quantitative baseline averages for human populations. Recent development of noninvasive 3D imaging technologies has advanced the speed, reliability, and precision of anthropometric data collection to efficiently establish norms for a cohort of individuals. Clinicians and surgeons have utilized 3D technologies to benefit patients of different genders, ages, and diverse ethnic and racial backgrounds undergoing procedures to improve upon facial aesthetics and function. Within the field of dentistry, the assessment of facial measurements using 3D imaging has also been useful for orthodontic treatment plans or for the surgical correction of craniofacial anomalies, including cleft lip and palate.

Historically, soft tissue measurements for Malaysian Malay individuals have been poorly defined in the literature and require further characterization to advance patient treatment plans. At the University of Malaya in Kuala Lumpur, Malaysia, there is a desire to expand upon the oral and nasal measurements currently reported in the literature to acquire a more robust data set for the Malay ethnic group. This study aims to utilize 3D imaging and analysis to establish and compare the lip-nose complex norms for males and females of pure Malay lineage.

A cohort of 50 males and 50 females between the ages of 18 to 30 years of pure Malay ancestry was enrolled in this study. A VECTRA-3D Facial System was used to photograph a 180° frontal image of each patient with their lips in their relaxed state. 3D Mirror Software was then used to measure 12 linear distance measurements of the oral and nasal regions for each subject. Nostril and philtral shapes were also characterized.

The mean and standard deviations for the oral and nasal measurements were calculated for Malay males and females. An independent t-test was used to compare males to females within the Malay ethnic group. A chi square test showed no significant differences between males and females for frequency or distribution of philtral shape ($X^2= 5.2$ with p value=0.517) or nostril shape. A t-test was also used to quantify the differences between Malay measurements from other ethnic group data, recorded in anthropometric literature (Indian, Chinese, Caucasian, and Black). Full statistical analyses still need to be performed.

Characterizing the delayed dimensional changes for gypsum dental stone material**Ivandario Saldarriaga****Harvard School of Dental Medicine, Oliver Wendell Holmes, Class of 2017****Sang Lee, DMD****Department of Prosthodontics,
Harvard School of Dental Medicine**

Gypsum stone is used in dental settings to make molds of patients' oral cavities. Gypsum is mixed with water to create a solid dental stone which is then a replica of a patient's teeth and gingiva. These molds need to be accurate in order to provide precise treatment planning. The dental stone molds are used in clinical laboratories to build dental prosthetic appliances that can accurately fit in a patient's mouth. Despite gypsum's ease of use and very low cost, challenges arise because of the material's inherent setting properties. The expansion standards established by American Dental Association (ADA) are only for the first two hours after setting although expansion can occur up to 75 – 100 hours after mixing. The expansion can cause inaccuracies in the fit of prosthodontic appliances, such as implants, bridges, or dentures. This project will characterize the delayed expansion of Type 4 (high strength, low expansion) gypsum stone material (FujiRock) which is commonly used at Harvard School of Dental Medicine's clinics.

This project will utilize an anatomical model made of gypsum to observe the volumetric dimensional changes in the model, the linear dimension changes and angle changes between implant scan bodies. Digital volumetric scans were taken of fifteen samples using an extra-oral Straumann 3D scanner. The scans occurred on daily intervals up to 96 hours after setting. Expansion seen at 2 hours should be within ADA requirements; however, the gypsum material is expected to continue to expand after the 2 hour mark and exceed the ADA expansion limits 96 hours after mixing. The samples are expected to demonstrate volumetric, linear and angular changes after the initial two hours.

I was able to assist with the manufacturing of the fifteen anatomical gypsum samples. Each of the fifteen models had four scan bodies embedded to facilitate with the scanning process and to represent the positions of implants. I scanned the models and used the generated data file for analysis using 3D rendering software (Geomagic Qualify 2012). With the software I was able to get information on spatial analysis as well as linear and angular changes between the scan bodies.

The results of this study will assess the delayed expansion that could distort models. Our protocol will capture the volumetric changes observed in real gypsum oral models using three-dimensional scanning software. Due to the scope and timeline of this project, we were limited to studying a single gypsum product.

SIRT6: A potential neuroprotective gene against PD pathology**Alireza Samiei****Harvard Medical School, Irving London Society, Class of 2017****Mel Feany, MD, PhD****Department of Pathology, Harvard Medical School
Brigham and Women's Hospital**

Parkinson's disease (PD) is the second most common neurodegenerative disease. Patients typically present with a range of movement impairments, such as bradykinesia, rigidity, and tremor. At the tissue level, there is evidence of neurodegeneration in a number of different brain regions, particularly among the dopaminergic neurons of the midbrain. It has been long known that there are groups of dopaminergic neurons that are resistant to neurodegeneration. Here, we aim to elucidate the molecular distinctions that render groups of dopaminergic neurons resistant to PD-induced neurodegeneration. To this end, we carried out a microarray data meta-analysis and identified *SIRT6* as a candidate neuroprotective gene in resistant dopaminergic neurons. This gene codes for a histone deacetylase that is highly expressed in the brain and has been shown to regulate genome stability, DNA damage repair, and telomere integrity. We hypothesized that constitutive *SIRT6* expression levels negatively correlate with the onset of neurodegeneration in midbrain dopaminergic neurons following PD's neurodegenerative insults. We chose the *Drosophila melanogaster* as the model organism to test our hypothesis. *Drosophila*'s central nervous system has well-studied clusters of dopaminergic neurons that show differential vulnerability to pathology in established *Drosophila* models of PD. We created three *SIRT6* knockdown *Drosophila* lines and aged the flies to up to 60 days. We monitored the flies' climbing ability at different ages to study the potential effect of decreased SIRT6 translation on the flies' locomotion. While two of the lines showed no apparent phenotype, one group had diminished climbing ability with aging. Currently, we are carrying out immunohistochemical studies to look for potential pathology in the dopaminergic clusters of these fly lines. Specifically, we are going to evaluate the levels of DNA damage, apoptosis markers, dopamine production, and histone deacetylation (H3K56) in these neuronal clusters. We expect that down regulation of SIRT6, particularly in the phenotypic line, will increase basal DNA damage level, reduce dopamine production, and render a group of dopaminergic neurons more susceptible degeneration. Our promising behavioral finding has prompted us to create a total *SIRT6* knockout and knock in *Drosophila* lines to determine whether modulating *SIRT6* expression levels correlates with altered health and activity of dopaminergic neurons in both wild type and a PD model flies. Our long-term goal is to study a potential causative role between SIRT6 expression/activity levels and resistance to PD pathology in dopaminergic neurons of *Drosophila*. We hope that an appreciation of *SIRT6* pushes the boundaries of PD research.

Ultrasound for Brain Shift Monitoring**Rahul Sastry****Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017****Alexandra Golby, MD****Department of Neurosurgery****Brigham & Women's Hospital**

Currently, the standard of care for primary brain tumors is surgical removal with image guided approaches. Brain shift, which can be caused by swelling, gravity, tumor resection, CSF drainage, and many other factors, is a well-characterized phenomenon that greatly diminishes the usefulness of pre-operative imaging. In the absence of updated intraoperative imaging, surgeons must estimate the size and direction of shifts intraoperatively, which is challenging and imprecise at best. Given the limitations, cost, and low availability of intraoperative MRI systems, it is apparent that updated intra-operative imaging, which makes use of quickly acquired imaging modalities to update preoperative images with intraoperative deformations, could be a novel, cost-effective, and information-rich tool for neurosurgeons.

Our proposed solution involves an early intra-operative, pre-resection Ultrasound (US) scan, obtained before the opening of the dura, and a series of intra-operative US scans obtained during the resection. Three-dimensional US Volume reconstructions will then be created from the two-dimensional US scans and non-rigidly registered to each other. The computed non-rigid deformations, which represent intra-operative brain shift, can then be used to update the pre-operative MR scan and create a *computed* intra-operative MR image for the surgeon.

To create and validate this proposed approach, MRI and US data were analyzed from 15 patients who underwent glioma resections at the AMIGO suite in the Brigham & Women's Hospital in 2013 and 2014. Thus far, we have developed and implemented a robust method of US volume reconstruction based on the Public Software Library for Ultrasound Research (PLUS) volume reconstruction methods. Our updated algorithm dynamically finds the region of every acquired ultrasound frame that contains meaningful information and excludes the remaining dark areas, effectively eliminating outlier frames that would otherwise diminish the quality of the reconstructed volume.

Image volumes have successfully been constructed for all available cases in the dataset, and preliminary inspection suggests that brain shifts can be visualized with 3D ultrasound reconstructions; however, much future work is necessary in order to determine if observed images can be reliably registered into the same reference space as the MRI. The next step in the analysis is to establish a reliable protocol for handling irregularities in probe tracking data in order to facilitate registration of US to MR images in a common coordinate system. After doing so, we will evaluate multiple deformable registration algorithms for the quantification of brain shift. The various algorithms will be evaluated by a Target Registration Error compared to a gold-standard of anatomical correspondences as labeled by a neuroanatomist.

Oncology Drug Development: Phase II Trial Design
Emily Schapira

Harvard Medical School, William Bosworth Castle Society, Class of 2017
Alexandra J. Miliotis Fellowship in Pediatric Oncology

Elizabeth B Lamont, MD MS
Department of Medicine and Healthcare Policy, Harvard Medical School

An improved understanding of cancer biology has resulted in identification of new therapeutic targets and supported oncology drug development. Experimental therapeutics showing preclinical promise progress through sequential stages of clinical trials. Phase I studies are primarily dose determining and open to patients with many tumor types. The single-armed Phase II trial generally evaluates efficacy in a single tumor type to determine whether the drug merits further examination in a Phase III trial. Phase III studies compare results of drugs found to be promising in phase II trials against current standards of care. While each phase is subject to its own inherent limitations, phase II limitations are of particularly important consequence as their results are often the key determinants as to whether therapies go on to be approved through the FDA's Accelerated Approval program, studied in large-scale phase III trials, or not recommended for further evaluation. At their best, Phase II trials minimize both Type I errors (i.e., falsely concluding a treatment is efficacious when it is not or a false-positive result) and Type II errors (i.e., concluding a treatment is not efficacious when it is or a false-negative result). However, existing literature suggest that positive results from Phase II oncology trials frequently are not replicated in the Phase III setting, an example of a Type I error. We examined current literature to comprehensively describe the most significant vulnerabilities in the phase II trial design.

Flaws in phase II trial design may limit the generalizability of data and artificially inflate or deflate the apparent efficacy of drugs. Phase II trials in oncology tend to be single-armed trials that rely on comparison of response rate to historical controls. The use of historical controls is problematic: it ignores changing standards of care over time and variability in prognostic characteristics between groups of patients. Improvements in imaging and supportive care over time alter patient outcomes independently of changes in therapy. Furthermore, results in non-randomized trials are highly dependent on the prognostic characteristics of enrolled patients. Even known prognostic variables (age, income, performance status) account for only a small portion of the variation observed between patients, and new prognostic variables, such as travel distance to the site of care, have recently been described. Adoption of a randomized phase II trial design would address many of the issues associated with current phase II trials and result in a decreased the rate of Type I errors.

Social Emotional Functioning in Active and Weight-Recovered Anorexia Nervosa**Cindy B. Schmelkin****Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017****Elizabeth A. Lawson, MD MMSc
Neuroendocrine Unit, Department of Medicine
Massachusetts General Hospital**

Social emotional deficits, including social anxiety, alexithymia, and difficulty recognizing emotions in others, have been described in anorexia nervosa (AN). Whether these represent an endophenotype (increasing illness risk and persisting as a trait marker), or exist due to starvation as a state marker associated with more severe illness (that may persist as a scar), is not understood.

We therefore investigated the effects of weight recovery and self-reported lowest adult body mass index (BMI; as a proxy for illness severity) on social emotional function in women with *DSM-5* AN. We examined 38 active AN, 41 weight-recovered AN (ANWR), and 44 healthy controls (HC). Height and weight were assessed and participants completed the Dimensional Assessment of Personality Pathology–Basic Questionnaire: Suspiciousness and Inappropriate Attachment subscales, Leibowitz Social Adjustment Scale–Self Report, and, in 63 subjects, the Toronto Alexithymia Scale. BMI was similar in ANWR and HC.

AN and ANWR did not differ in suspiciousness, difficulty identifying feelings, and alexithymia; both groups reported greater difficulties than HC ($p < .005$). ANWR reported social and public fear intermediate between AN and HC ($p < .02$), whereas social and public avoidance was increased in AN ($p < 0.003$), but did not differ between HC and ANWR. AN reported greater insecure attachment than HC ($p = .008$), and ANWR did not significantly differ from either group. Lowest BMI in AN (but not ANWR) was negatively correlated with social fear ($r = -0.64$), social avoidance ($r = -0.59$), public fear ($r = -0.51$), and public avoidance ($r = -0.56$) ($p < 0.003$), independent of current BMI, and was not associated with other social emotional measures.

These data show that social emotional deficits in AN only partially improve with weight restoration and may be more pronounced in those with the most severe illness. Further studies are needed to determine whether these social deficits are a cause, correlate, or consequence of AN.

Management of Chronic Opioid Users at MGH Chelsea – Adult Medicine**Kristan A. Scott****Harvard Medical School, Francis Weld Peabody Society, Class of 2017****Marya Cohen MD, MPH****MGH Chelsea Health Center, MGH General Medicine Division**

It is estimated that 116 million patients in the United States suffer from chronic pain. Prescription opioids have dominated other treatment modalities like physiotherapy and non-narcotic pain medications in addressing this issue. As a result, many physicians face the predicament of how to provide quality care to patients with chronic pain while balancing potential negative effects of opioid therapy, such as addiction and diversion. In response, the MGH Chelsea Adult Medicine clinic has instituted guidelines for the chronic use of opioids. To better understand and ensure the implementation of the opioid policy, the management of chronic opioid users at the clinic has been reviewed and analyzed.

A retrospective chart review was performed using Partners HealthCare's Research Patient Data Registry (RPDR) to retrieve data for patients that received a prescription for opioids between November 2013 and February 2014. Chronic opioid users were defined as those patients who consistently used opioids for more than 90 days. To further characterize the population, data obtained from chart reviews included age, gender, reason for prescription, and medical comorbidities. Management tactics, such as signing a narcotics contract, and other variables were included in the data to assess proper management. Patients were excluded from the chart review based on the following criteria: cancer-related pain; stable opioid-replacement therapy; utilization of out-of-state pharmacies. Ultimately, each provider at the clinic was provided with a summary list of his or her chronic opioid user patients from the data collected in this chart review.

After reviewing 1421 patient charts, 618 patients fit the criteria of chronic opioid use (ie, had prescriptions greater than 90 days). Their average age was 57, and back pain was the principal reason for prescription. A narcotics contract was in place for 34% of the patients. Urine toxicology screens were performed on 43% of the patients, with 18% having a screen within the past six months. Patients were 2.9 times more likely to have a urine toxicology screen performed and 7.6 times more likely to have the screen performed within the past six months if a narcotics contract was in place ($p < .05$).

The data suggests that signing a chronic opioid user agreement improves provider utilization of proposed management tactics. Patient summaries will help providers identify their chronic opioid user patients and institute the recommendations of the MGH opioid policy. Future directions include developing educational materials for the chronic opioid using patients.

***Ex vivo* manufacture of transfusion-quality erythrocytes from human induced pluripotent stem cells**

Akash A. Shah

Harvard Medical School, William Bosworth Castle Society, Class of 2017

George Q. Daley, MD, PhD

**Stem Cell Transplantation Program, Department of Hematology/Oncology
Boston Children's Hospital**

Red blood cell (RBC) transfusion is the most common procedure performed in hospitals. There is a pressing need to generate complementary sources of RBCs for transfusion to address supply constraints and mitigate the adverse effects associated with allogeneic transfusion (e.g. allo-immunization against RBC antigens). *Ex vivo* manufacture of RBCs from induced pluripotent stem cells (iPSCs) provides an opportunity for safe and sufficient transfusion.

While investigators have been able to generate transfusion-quality RBCs from CD34+ progenitors found in cord blood, these progenitors have limited self-renewal capacity. On the contrary, iPSCs represent an inexhaustible source for derivation of RBCs. Here, we attempt to generate transfusion-quality erythrocytes from human iPSCs.

Previous efforts to differentiate iPSCs to RBCs have not been successful in generating mature RBCs with a high enucleation efficiency and adult globin. We employ a novel approach, differentiating mesenchymal stem cell-derived iPSCs (MSC-iPSCs) to myeloid lineage-restricted progenitors and respecifying these progenitors to definitive hematopoietic stem cell (HSC)-like cells with a cocktail of 5 transcription factors (HOXA9, ERG, RORA, SOX4, MYB). We then differentiated the HSC-like progenitors to RBCs using a stepwise erythroid differentiation protocol. We did not observe efficient enucleation *in vitro*.

Hypothesizing that an *in vivo* niche may stimulate enucleation, we transplanted 10^6 HSC-like progenitors into the bone marrow of NOD-SCID mice and observed whether this resulted in increased enucleation. After 4 weeks, we bled the mice retro-orbitally and sorted for human RBCs; we observed only 4.3% enucleation. We then transfused 10^8 RBCs differentiated from MSC-iPSC-derived HSC-like progenitors into the peripheral blood of a NOD-SCID mouse. We collected RBCs through retro-orbital bleeds at 24 hours and 48 hours post-transfusion and sorted for human RBCs. A significant improvement in enucleation efficiency was observed: 97.6% enucleation after 24 hours and 94.7% enucleation after 48 hours.

This is the highest enucleation efficiency reported for iPSC-derived RBCs and represents an important first step toward *ex vivo* manufacture of transfusion-quality RBCs from iPSCs. We are currently analyzing the functionality and globin status of these recovered iPSC-derived RBCs.

Oral Health Knowledge and Behaviors of Latina Mothers -a Pilot Study**Taavish Sharma****Harvard School of Dental Medicine, Walter Bradford Cannon Society, Class of 2017****Tamanna Tiwari, MPH MDS BDS****University of Colorado School of Public Health****Center for Native American Oral Health**

Latino children have among the highest rate of untreated tooth decay among all racial and ethnic minorities in the United States. Numerous studies have looked at risk factors of oral disease and early childhood caries in Latino populations, yet very few elucidated underlying protective factors and oral health attitudes, knowledge and behavioral patterns. This pilot study aimed to describe protective oral health knowledge and oral health behaviors in Latina mothers with children under 6 years of age to ascertain need for long term educational and interventional goals.

A convenience sample of Latina mothers was enrolled from University of Colorado Children's Hospital. This study used a mixed methods explanatory design: quantitative data was collected and analyzed, with qualitative data subsequently collected and analyzed to elaborate on quantitative findings. All 30 participants completed a portion of the Basic Research Factors Questionnaire (BRFQ) and 10 mothers participated in focus groups. The means and standard deviations were calculated for the overall behavior and knowledge scores, and further stratified by birth order. The qualitative data from focus groups was transcribed and analyzed using a grounded theory approach.

The overall average behavior score on the BRFQ was 42 percent and the overall knowledge score was 79 percent for the study participants. Though the quantitative knowledge scores were relatively high, mothers had seemingly superficial oral health knowledge in focus groups. Common microorganism based causes for dental caries and the preventative role of fluoride were relatively unknown. The overall maternal oral health behavior scores were quite low and mothers pointed out several barriers in maintaining oral health for their children, including cultural differences, child's temperament, and access to high risk foods. Lastly, all participants wanted to receive more information on improving the oral health of their children from medical and dental providers.

Though mothers recognized some of factors related to caries development, their knowledge was limited in depth, which limits development of caries prevention behaviors. Comprehensive and culturally appropriate oral health education may have a strong impact on this population, including caries prevention, oral hygiene maintenance, and diet, which could lead to increased oral health behavior and higher sense of self-efficacy in Latina mothers with respect to their children's oral health. The primary limitation in this study was the small convenience sample obtained over a very short data collection window. However, consistency and saturation of qualitative results supports exploring avenues for oral health promotion in this population.

Uncovering the Mechanism of Salivary Opiorphin's Antinociceptive Effect**Cristina Shea****Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017****Clifford Woolf, MB, BCh, PhD****Department of Neurobiology****Boston Children's Hospital**

Pain is a huge socioeconomic problem that impairs lives and creates a heavy economic burden on healthcare systems and society. One approach to devising new therapeutic strategies is to study the properties of pain-relieving compounds endogenous in humans. In 2006 a human salivary pentapeptide with analgesic properties, named 'opiorphin,' (QRFSR) was reported. It was hypothesized that opiorphin acts by slowing the breakdown of endogenous opioids. Our lab has shown that opiorphin may inhibit pain instead by antagonizing TRPV1 channels in peripheral nociceptors. A localized analgesic effect of opiorphin in saliva is supported by the innate wound licking behavior observed in many animals.

This summer project, aimed at further characterizing the antagonistic effect of opiorphin on TRPV1, had two goals: 1) to create dose-response curves to determine the type of antagonism (competitive vs. non-competitive), and 2) to conduct structure-function studies to determine which amino acids are critical to the peptide's antagonistic behavior.

To complete aim 1, TRPV1 activation in HEK cells transfected with TRPV1 was measured with a calcium flux assay on a Hamamatsu apparatus. Activation was measured with increasing concentrations of capsaicin (a selective TRPV1 agonist) in the presence of various opiorphin concentrations. Increasing opiorphin concentrations were associated with a decrease in the maximum response to capsaicin but no shift in EC50, suggesting opiorphin acts as a non-competitive antagonist.

To complete aim 2, the antagonistic behavior on TRPV1 of synthetic opiorphin analogs, as well as naturally occurring human and rat analogs, was tested. TRPV1 activation in mice DRG cells was measured with a calcium flux assay on a Hamamatsu apparatus. Lack of antagonistic activity of two synthetic analogs (QKFSR and QRFSK) and good antagonistic activity of the naturally occurring human peptide QRGPR suggests the importance of the 2nd and 5th position arginines. Inactivity of the human peptide QRLDLR suggests that the two amino acid distance between the arginines is critical to the antagonistic behavior of opiorphin. Further structure-function experiments with synthetic analogs that differ from opiorphin at other positions are warranted. This study suggests that opiorphin acts as a non-competitive antagonist on TRPV1, and implicates key amino acids in opiorphin's antagonistic effect.

Voriconazole Phototoxicity in Children: A Retrospective Study

Johanna Sheu

Harvard Medical School, Oliver Wendell Holmes Society, Class of 2015

Society of Pediatric Dermatology Fellowship

Jennifer T. Huang, MD

Division of Dermatology, Department of Immunology

Boston Children's Hospital

Voriconazole, an antifungal agent, is associated with various cutaneous reactions, including phototoxicity, accelerated photoaging, and skin cancer. Incidence and risk factors for these reactions in children have not been well described.

The objective of our study was to determine the incidence of and factors associated with phototoxic reactions and non-melanoma skin cancer (NMSC) in pediatric patients treated with voriconazole. Our methods included a retrospective analysis of 430 pediatric patients treated with voriconazole between 2003 - 2013 at Boston Children's Hospital.

The incidence of phototoxicity was 20% in all children treated with voriconazole and 47% in children treated for 6 months or longer. Factors associated with phototoxicity included white race, cystic fibrosis, cumulative treatment time, and cumulative dose. Four patients (1%) had NMSC; all experienced a phototoxic reaction during voriconazole treatment. Of those with phototoxicity, 5% were discontinued on voriconazole, 6% were referred to dermatology, and 26% received counseling about sun protection from their primary physician.

Our study is limited by its retrospective design and potential referral bias associated with a tertiary-care center. Voriconazole-associated phototoxicity is relatively common in children and may lead to NMSC. However, those with phototoxic reactions are often continued on therapy, rarely referred to dermatology, and infrequently counseled on sun protection.

Preoperative Cognitive Screening in Elderly Surgical Patients**Connie R. Shi****Harvard Medical School, Walter Bradford Cannon Society, Class of 2017****Deborah J. Culley, MD****Department of Anesthesia****Brigham & Women's Hospital**

Cognitive assessment is absent from formal preoperative evaluation, despite evidence that preexisting cognitive impairment correlates with higher rates of postoperative complications, longer hospital stays, and higher 6-month mortality following elective surgery. This is of particular relevance for patients age 65+, among whom an estimated 20-25% have some degree of cognitive impairment. In this study, we used the Mini-Cog, a short screen for cognitive impairment (sensitivity 75-99%; specificity 81-93%) to cognitively stratify elderly patients presenting for preoperative evaluation before elective surgery at Brigham and Women's Hospital (BWH). The aims of this study were to determine 1) if the Mini-Cog is a reliable and feasible means of cognitive assessment in the context of a busy preoperative center, and 2) if results of the screen can predict and/or modify postoperative outcomes in this high-risk population.

500 patients over age 65 and scheduled for elective surgery at BWH completed the Mini-Cog prior to their preoperative evaluation (mean age 73). Mini-Cogs were administered by anesthesia residents (n=100), nurse practitioners (n=100), an undergraduate student with no medical training (n=100), and the study team (n=200). Participants were also surveyed about their perceptions of the value of pre-surgical cognitive testing. We collected patient baseline information including age, weight, education level, METs, and ASA physical status, along with information on outcomes of interest including length of preoperative evaluation, hospital length of stay, complication rate, and discharge location to investigate their relationship to Mini-Cog score. Univariate analysis was performed using Spearman correlation ($p < 0.05$ for statistical significance).

29% of participants had Mini-Cog ≤ 2 (positive screen for probable cognitive impairment). On univariate analysis, age (correlation coefficient CC -0.19), male gender (CC -0.15), education level (CC 0.12), ASA physical status (CC -0.13), and METs (CC 0.17) were statistically significant predictors of Mini-Cog ≤ 2 . Mini-Cog ≤ 2 was a statistically significant predictor of time required for preoperative evaluation (CC 0.18, $p = 0.003$), and discharge to place other than home (CC 0.14, $p = 0.002$). Consensus in scoring Mini-Cogs was above 83% for all administrators, indicating that this is a robust screen that can consistently be performed by individuals at varying levels of training. Perhaps most notably, the survey results suggested that patients support cognitive testing if it helps predict surgical outcome.

The Mini-Cog is a convenient, robust, and feasible means of assessing baseline cognitive function in the preoperative setting and shows promise as a predictor of postoperative outcomes for elderly surgical patients. The results of this study have already informed changes in preoperative care management at BWH, including implementation of a video module that trains clinical staff to conduct the Mini-Cog in preoperative visits. This study represents a critical step forward in our understanding of cognitive status, surgical risk, and postoperative outcomes in the elderly patient.

Establishment of a Robust Xenograft Mouse Model of IDH-mutant Glioblastoma**Diana Shi****Harvard Medical School, Walter B. Cannon Society, Class of 2017****William Kaelin Jr., MD****Medical Oncology, Dana Farber Cancer Institute**

Glioblastoma multiforme (GBM) is the most common and malignant form of brain cancer, with a median survival of approximately 14 months. Though novel treatments are urgently needed, lack of an effective *in vivo* model to test therapeutic strategies has been a significant obstacle.

Recent studies revealed that mutations in isocitrate dehydrogenase 1 (IDH1) are often present in secondary GBM tumors, a subset of GBM that progresses from a low-grade or anaplastic astrocytoma and follows a genetic pathway to malignancy distinct from primary GBM tumors. The goal of this project is to use mutant IDH1 and other known genetic variants present in secondary GBM to generate a transformed astrocytic cell line capable of forming gliomas when orthotopically xenografted into immunodeficient mice.

We first infected immortalized human astrocytes with a retrovirus encoding an oncogenic form of IDH1 or, as a control, with the empty virus. Following drug selection with hygromycin, these cells were infected with a second retrovirus encoding wild-type PIK3R1, one of three glioma-associated PIK3R1 mutants, or with empty virus. These cells were then selected with zeocin, resulting in ten stable daughter cell lines.

Next, we conducted soft agar assays on each of these cell lines to determine their anchorage-independent growth, a classic hallmark of transformation. Astrocytes expressing H-Ras were used as a positive control. In addition, we conducted growth assays with cells plated at low and high cell density to examine loss of contact inhibition and cell cycling defects. Astrocytes expressing either mutant IDH1 or the PIK3R1 mutants exhibited significantly increased colony size and number in the soft agar assay compared to the vector controls, and these phenotypes were enhanced further in the cells expressing both the IDH1 and PIK3R1 mutants compared to cells expressing either mutant alone. Similarly, a cooperative effect was seen in the high cell density growth assay, implying an increased loss of contact inhibition in the presence of both mutants.

We subsequently focused on the PIK3R1 mutant (DKRMNS560del) that was most capable of promoting transformation, alone and in combination with mutant IDH1, *in vitro*. Immortalized astrocytes expressing mutant PIK3R1 alone, mutant IDH1 alone, both, or neither, as well as the H-Ras positive control astrocytes, were infected with a luciferase-GFP construct and sorted with FACS. These cells were then injected intracranially into immunodeficient mice and are currently being imaged every seven days to monitor tumor growth. Based on the results of our *in vitro* assays and preliminary imaging data, we expect robust tumor growth in these mice that will ultimately serve as an effective animal model to test novel therapeutic strategies for IDH-mutant glioblastomas.

Inferior Turbinate Asymmetry in Unilateral Complete Cleft Lip and Palate**Daniel Sierra-Vasquez****Harvard School of Dental Medicine, Walter Bradford Cannon Society, Class of 2017****Bonnie Padwa, DMD, MD****Department of Oral and Plastic Surgery****Boston Children's Hospital**

Patients with unilateral complete cleft lip and palate (UCLP) have a characteristic nasal deformity typified by deviation of the caudal septum towards the cleft side. This narrows the nasal valve unilaterally, and may compromise air flow. The complex relationship between nasal airflow and turbinate size has previously been described. In patients with septal deviation, increased air flow through the contralateral nare triggers a process of compensatory hypertrophy in the mucosa surrounding the inferior turbinate of the unobstructed side. In patients with UCLP, hypertrophy of the inferior turbinate on the non-cleft side has been noted, with relative underdevelopment of the cleft-side turbinate. However, it remains unclear whether the discrepancy occurs as a reactive soft-tissue hypertrophy related to septal obstruction, or if a true bony asymmetry exists as part of the congenital structural deformity.

Previous studies of patients with UCLP have confirmed skeletal hypertrophy of the inferior turbinate on the side opposite the cleft. To date, no studies have characterized the bony turbinate on the cleft side or directly compared turbinate dimensions on the cleft versus non-cleft side. We propose a retrospective study of cone beam computerized tomography (CBCT) scans to measure hard- and soft-tissue dimensions of the inferior turbinate in patients with UCLP. We expect to find a significant difference in the maximum cross-sectional area of the cleft-side turbinate compared to the non-cleft side, and hypothesize that the former will be significantly smaller by comparison.

This is a retrospective radiographic study. Records for all patients with UCLP who had their primary repair performed at Boston Children's Hospital between 1988-2013 were reviewed. All subjects were operated on by a single surgeon and underwent lip-nasal adhesion with no correction of the septum at the time of primary closure. Non-syndromic patients who had a CBCT scan in the medical record were included in the study. Patients with a history of nasal revision or maxillary advancement procedures prior to the CBCT were excluded. On serial CBCT images, each turbinate was divided into an anterior, middle, and posterior third and the length, width, and cross-sectional area of each segment were measured bilaterally. Turbinate size was defined as the maximum cross-sectional area of the turbinate regardless of location along the rostro-caudal axis.

Currently the study sample includes 52 patients with non-syndromic UCLP. Data collection is complete and analysis is pending (SPSS Statistics 16.0, Chicago, Illinois, USA). A re-test correlation will be used to test measurement reliability and a paired t-test will compare bony turbinate dimensions on the cleft and non-cleft sides. Multivariate analysis also will be performed to control for the effects of age and gender. All analyses will be run using SPSS Statistics 16.0. We intend to publish or present the results of our work.

Mobile Health Technology in Kenya: Costs and Challenges of Implementing and Maintaining a Triage Application

Abhayjit Singh

Harvard Medical School, William Bosworth Castle Society, Class of 2017

Joseph C. Kvedar, MD

**Department of Dermatology
Massachusetts General Hospital**

The worldwide explosion of mobile phone usage has created a unique opportunity to transform the delivery of healthcare, particularly in low and middle income countries with otherwise inadequate access to care. Kenya, with an absolute poverty rate of 42% and 0.181 physicians per 1,000 people, ranks among the poorest and most underserved countries in the world. Nevertheless, Kenya's mobile coverage includes nearly 95% of the country's 44 million population, with 93% of Kenyans using mobile phones on a daily basis. These factors have made Kenya a prime target to uptake and utilize mobile health technologies.

Sana is one such mobile health technology. Developed at the Massachusetts Institute of Technology as an open-source and customizable mobile platform, Sana allows for real time communication between community health workers operating peripherally and centralized physicians, effectively expanding the reach of individual clinicians. The cellular phone application enables physicians to remotely triage patients into one of three categories (immediate hospital transfer, referral to outpatient clinic, or care at home) based on relevant information obtained by community health workers. In 2011, the Nairobi-based nonprofit Partners for Care (PFC) adopted this mobile health application for use in a community clinic that serves about 1000 households just outside Nairobi, before expanding the technology to a government health center in 2013. The goal of this project was to evaluate the effectiveness and cost of the mHealth project, both essential factors in potential scale-up.

Our evaluation revealed several significant challenges to the success of the Sana mHealth program. Chief among these were technical issues, both intrinsic and extrinsic to the project. The lack of a technically literate support team made it difficult to handle commonplace issues that arise when using such technologies. Additionally, power outages, limited internet connectivity, and inadequate infrastructure in resource-poor settings stunt the effectiveness of mobile health programs. Ideally, mHealth technologies will have dedicated technical support and requirements reflective of their settings.

Furthermore, we uncovered and characterized the costs associated with the implementation of maintenance of the mHealth program. Costs of implementing Sana were divided into categories of infrastructure (computer, cellular phones, CHW supplies, server space) and services development time, administrative implementation, training of CHWs and physicians), while the maintenance of Sana required functional costs (server, phone data, internet) and personnel costs (CHW and physician hours, technical support). We hope these findings not only improve PFC's existing mHealth program, but will also inform future mobile health projects.

Code Voices: An Audio Narrative of In-Hospital Cardiac Arrest

Samuel D. Slavin

**Harvard Medical School, Walter Bradford Cannon Society, Class of 2017
Ghiso Fellowship in Compassionate Care**

**Jeffrey Rothschild, MD, MPH
Associate Professor of Medicine
Harvard Medical School**

When a patient goes into cardiac arrest most hospitals activate a coordinated response called a “code blue” or simply a “code.” For the most part, popular media depict codes as quick and highly successful, while recently there has been an opposing trend in the media and the medical community to emphasize their violence and futility. Yet both depictions often miss the subtleties and emotional truths of how hospital staff, patients and their families experience these events.

We recorded 25 hours of interviews with the full range of staff and families that we will edit to create a 20-minute audio documentary. By weaving together personal stories from diverse perspectives, we aim to provide the medical community and the general public with a nuanced and intimate account that may inform approaches to end-of-life care.

In the first phase of the project, we recorded, transcribed and annotated 28 interviews with nurses, physicians, chaplains, housekeeping staff, patient care techs (nurses aides), a unit coordinator and a pharmacist, as well as family members of patients who were resuscitated. In the second phase, we will edit the interviews, record narration, and incorporate additional elements, such as ambient sound and music.

The final audio piece will follow the chronology of a typical code blue event incorporating multiple voices and experiences at each stage. Themes may include first experiences with codes, leading a code, grappling with futility, interaction between family and staff, interactions among staff, moments of humor, emotional processing and coping. An overarching theme will be that of a shared human experience that transcends different roles and relationships to the patient.

**Modifiable Risks for Hospitalization in Children with
Neurological Impairment**

Hannah Song
Harvard Medical School, William Bosworth Castle Society, Class of 2017

Keith Van Haren
Department of Child Neurology
Stanford Medical School

Children with neurological impairment (NI) represent a diverse group of individuals who account for a third of all costs at children's hospitals. Standardizing and refining care strategies for these children have the potential to reduce health care costs and increase the quality of life for these children.

The main objective of the study was to examine the differences in hospitalization rates for ambulatory sensitive conditions for children with NI. Many studies group children with NI into one broad category, but we do not know whether and how the hospitalization patterns change, depending on the specific disorder. Therefore, we determine the hospitalization rates for ambulatory sensitive conditions in patients with three different NI—cerebral palsy, epilepsy, and chromosomal abnormalities. We hypothesized that the hospitalization rates would be similar across the different subgroups, and that we would therefore be able to assess outpatient interventions that apply to a greater population of NI pediatric patients.

We used the California Children Services database between the years 2010-2012 to identify children with cerebral palsy, epilepsy and chromosomal abnormalities based on previously established ICD-9 diagnostic codes for these cohorts. We limited the search to patients between 1 year and 18 years of age who were enrolled for at least 12 months. We used the ICD-9 diagnostic codes to determine hospitalization rates for ambulatory sensitive conditions, as defined by American Healthcare Research and Quality Indicators, in these three groups.

The three most common ambulatory-sensitive conditions that accounted for hospitalizations in all three groups were seizures, pneumonia, and dehydration. The percentage of hospitalizations for the ten most common ambulatory sensitive conditions between 2010-2012 for patients within each of the cohorts of cerebral palsy, epilepsy, and chromosomal abnormalities were 50.5% (n=11,191), 89.2% (n=8,126), and 27.3% (n=1,284) respectively. The differences suggest that different groups of pediatric patients with NI may be at different risks for inpatient hospitalizations. The pneumonia hospitalization rates between 2010-2012 for children with cerebral palsy, epilepsy, and chromosomal abnormalities were 11.8% (n=11,191), 14.4% (n=8,126), and 6.4% (n=1,284). Pneumonia is a common problem among major subgroups of children with NI.

The next steps of analysis include analyzing the factors that impact hospitalization rates. Different subgroups of NI have different rates of hospitalization for the same condition, suggesting that different clinical strategies may be warranted. We will next assess outpatient interventions that can impact hospitalization rates among high-risk subgroups.

The major limitation of the study was the overlap between the cohorts. There are patients with multiple conditions, such as epilepsy and cerebral palsy. The second major limitation of the study is that ICD-9 codes do not capture the severity of the disease, when the severity of the disease is an important indicator of the risk for hospitalization.

Head and Neck Malignant Melanoma: Assessing local and regional recurrence rates following wide local excision in immediate vs. delayed reconstruction

Jie Sun

Harvard School of Dental Medicine, Francis Weld Peabody Society, Class of 2017

Samuel J. Lin, MD

Division of Plastic Surgery

Beth Israel Deaconess Medical Center

Harvard Medical School

The incidence of cutaneous malignant melanoma has increased tremendously over the past 3 decades. Cutaneous malignant melanoma is the major cause of skin cancer-related deaths and approximately 20% of these tumors are found in the head and neck region. Excision of head and neck melanoma often involves risk of damaging critical structures, which could limit excision margin and lead to increased local recurrence. Currently, the standard of treatment for patients with melanoma includes wide local excision (WLE) with a safety margin. The timing of reconstruction (immediate vs. delayed) after wide local excision is debated due to local recurrence concerns. Delayed reconstructions is performed after review of final pathology and confirmation of negative margin status due to concern of incomplete excision, while immediate reconstruction is performed without review of final pathology. Our purpose was to evaluate the recurrence rates following wide local excision of head and neck malignant melanoma in immediate versus delayed reconstruction within 1 and 5-year follow-up.

We performed a retrospective analysis of the medical records of 451 head and neck melanoma patients at Beth Israel Deaconess Medical Center over a period of 20 years (1994-2014) and included 207 patients who underwent wide local excision and had at least 1 year of follow up for analysis. Reconstruction was immediate for 142 patients and delayed for 65 patients. In preliminary data analysis, local recurrence was reported in 19.7%(1-year) and 25.0% (5-year) of patients with immediate reconstruction, compared to 3.1%(1-year) and 20.7%(5-year) of those with delayed reconstruction. Regional recurrence rates in patients with immediate reconstruction were 2.8% (1-year) and 16.3%(5-year); Regional recurrence rates in patients with delayed reconstruction were 0.0% for both 1-year and 5-year follow-up in our patient population. Nodal recurrence rates were 6.3% (1-year) and 3.8%(5-year) in patients with immediate reconstruction, and 3.1% (1-year) and 0.0%(5-year) in patients with delayed reconstruction.

These preliminary data analysis results indicate that local recurrence rates were consistently lower in patients with delayed reconstruction compared to those with immediate reconstruction. Patients undergoing delayed reconstruction also had lower rates of metastasis (satellite/in-transit, regional lymph node, distant) at the time of operation and at 1-year and 5-year follow-up after surgery compared to those with immediate reconstruction. We will conduct more statistical analyses by using chi-square analyses for categorical variables, t-tests for continuous variables, and Kaplan-Meier analyses to assess recurrence over time.

The Effect of IL-10 and TGF- β 1 in a Mouse Periapical Lesion Model**Kevin Sun****Harvard School of Dental Medicine, William Bosworth Castle Society, 2017****Hajime Sasaki, DDS, PhD****Department of Immunology and Infectious Diseases****The Forsyth Institute**

IL-10 KO and TGF- β 1 KO mice are susceptible to periapical lesions via up-regulation of IL-1 α , suggesting that IL-10 and TGF- β 1 seems to be important endogenous suppressor of IL-1 α . However, no study has yet determined whether the induction of IL-10 and TGF- β 1 has a therapeutic potential in the treatment of periapical lesions. The goal of this study was to determine the effect of the anti-inflammatory cytokines IL-10 and TGF- β 1 in regulating the levels of IL-1 α and TNF α produced by lipopolysaccharide (LPS) stimulated RAW264.7 cells. We hypothesized that IL-10 and TGF- β 1 treatment would down-regulate TNF α and IL-1 α production.

RAW264.7 cells (1×10^5 cells/well in 96-well plates) were stimulated with *E. coli* LPS (0.1 μ g/ml) for 24 hours in presence/absence of IL-10 (5 ng/ml and 0.5 ng/ml) and TGF- β 1 (1.5 ng/ml and 0.15 ng/ml). The timing of cytokine treatment was one hour before, at the same time, or one hour after LPS stimulation. LPS-stimulated cells without cytokine treatment served as positive controls. The level of proinflammatory cytokines (IL-1 α and TNF α) in the cell culture supernatants was determined by ELISA in triplicates. A non-paired student's t-test at a significance level of 0.05 was used to determine if a significant difference in the production of proinflammatory cytokines existed between the treatment and control groups.

Overall, both IL-10 and TGF- β 1 were capable of down-regulating LPS-stimulated proinflammatory cytokines *in vitro*. In particular, 5 ng/ml of IL-10 reduced the production of IL-1 α and TNF α to the baseline level in all treatment regimens ($p < 0.05$ vs. positive controls, respectively). On the other hand, we observed that the pre-treatment of TGF- β 1 consistently inhibited proinflammatory cytokines in a dose dependent manner. Pre-treatment of TGF- β 1 (1.5 ng/ml) resulted in a 68.8% reduction of IL-1 α and a 48.7% reduction of TNF α compared to positive controls ($p < 0.05$, respectively). Macrophages are the key regulatory cells in periapical inflammation via production of proinflammatory cytokines. Therefore, these findings led us to the second aim, to determine the effect of local injection of adenoviral vectors transducing either IL-10 or TGF- β 1 in a mouse periapical lesion model. Our hypothesis is that adenovirus mediated transduction of IL-10 and TGF- β 1 suppresses proinflammatory cytokine production and attenuates periapical bone resorption. We are currently conducting *in vivo* studies and expect to obtain results and conclusions in November 2014. Thus far, our results suggests that local overexpression of anti-inflammatory cytokines is an effective approach in controlling the development of periapical lesions.

Genetic Basis of Resistance to Lassa Fever in West Africa**Shervin Tabrizi****Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017****Pardis C. Sabeti, MD, DPhil****Associate Professor, Department of Organismic and Evolutionary Biology,
Harvard University****Senior Associate Member, Broad Institute of MIT and Harvard**

Lassa virus has the unique status of being both one of the world's deadliest pathogens, designated bio-safety level 4 (BL-4), and a public health crisis, endemic in large parts of West Africa. It is estimated to have originated over 1000 years ago in Nigeria, and a genome-wide survey of human variation identified the gene *LARGE*, biologically linked to Lassa virus infection, as among the strongest signals of natural selection in the Yoruba population of Nigeria.

We pursued the hypothesis that Lassa virus is an ancient selective force driving the rise of genetic resistance, by conducting a genome-wide association study (GWAS) of 641 Lassa fever cases and 2039 controls in Nigeria and Sierra Leone. We report a signal of association at *LARGE* with a protective effect for the haplotype under selection ($P=0.014$, $OR=0.71$ [0.55-0.94]). This suggests recent evolution of resistance to Lassa fever in West Africa, making it one of only a handful of known loci under positive selection elucidated to be involved in resistance to infectious disease.

Population genetics analysis provides further insights into the origins and spread of the resistance variant in *LARGE*. We show that the same putatively protective haplotype under selection in the Yoruba is also present in the Esan population of Nigeria and the Mende population of Sierra Leone. We find that the frequency is highest in the Yoruba (31%) and lower in the Esan (23%) and the Mende (19%). Its frequency is lowest in the Gambian population in West Africa (10%), where Lassa fever is not endemic, suggesting regional adaptation to the pathogen.

Beyond *LARGE*, our other top GWAS signals fall at genes not previously implicated in Lassa fever pathogenesis but which may play a role in modulating immune response to the virus, including our top signal at FAM135B, a gene of unknown function with evidence showing it may affect NF- κ B signaling, a central transcription factor in immune pathways. We also examine signals of adaptation in the Esan and Mende populations and the genetic relationship between these and other West African populations, providing new insights into human diversity and adaptation in West Africa.

This work is one of only a few surveys of genetic diversity in West Africa, a region underrepresented in GWA studies. It is also the first ever GWAS on a BL-4 agent, and demonstrates a novel genomics approach to understanding the world's deadliest pathogens.

Evaluating the Frequency of Artifacts in 3D Spectral-Domain Optical Coherence Tomography Images of the Optic Nerve

Andrew Taliaferro

Harvard Medical School, William Bosworth Castle Society, Class of 2017

Teresa Chen, MD

**Glaucoma Service, Department of Ophthalmology
Massachusetts Eye and Ear Infirmary**

Glaucoma is the world's leading cause of irreversible blindness. With spectral domain optical coherence tomography (SD-OCT) technology, we are now able to image the optic nerve in 3D. Over the past decade, high density 3D SD-OCT optic nerve imaging has replaced 2D time domain OCT imaging.

We have developed a new automated segmentation algorithm that quantifies the amount of optic nerve tissue in 3D SD-OCT images of the optic nerve, which is the primary site of damage in glaucoma. This new 3D parameter is called the minimum distance band (MDB). Preliminary data suggest that this 3D MDB measurement is better than 2D parameters for glaucoma diagnosis and for monitoring of disease progression. Despite this potential for improved glaucoma care, this new MDB parameter needs to be tested for artifact rates, because a better test may be limited by high rates of artifacts. Since the rate and types of artifacts seen with the MDB parameter is unknown, our study sought to classify and quantify these artifacts, providing an improved understanding of the potential for MDB segmentation errors.

This retrospective study was performed using Spectralis® (Heidelberg Engineering, Heidelberg, Germany) SD-OCT scans of 35 normal and 45 primary open-angle glaucoma patients, who were seen at the Massachusetts Eye and Ear Infirmary Glaucoma Service. One eye from each patient was included in the study. Since 193 B-scans comprised a single 3D image of the optic nerve, 15,440 B-scans (or 193 B-scans per patient) were evaluated for the presence of artifacts. Artifact type and frequency were determined.

Artifacts were classified broadly into two groups: systemic or localized. Systemic artifacts were associated with poor segmentation throughout the entire scan, including myopia-, blood vessel-, and decentration-related artifacts. Among these, improper centration of the optic nerve head was the most common (64% of normals, 60% of POAGs), followed by blood vessel-related artifacts (56%, 18%), and myopia-related artifacts (6%, 2%). Localized artifacts were those which could be identified within individual B-scans, such as optic nerve surface (ONS) misidentification (62%, 62%), retinal pigment epithelium (RPE) misidentification (35%, 31%), incomplete identification of the ONS (6%, 2%) or RPE (0%, 2%), and B-scan inversion (3%, 0%). In summary, we found that 1.8% of all B-scans evaluated contained at least one artifact.

Thus, although artifact frequency is low, MDB segmentation is particularly prone to decentration-related artifacts and ONS misidentification. Future improvements in this MDB algorithm should attempt to correct these issues.

Development and implementation of clinical pathways in lung cancer at an academic comprehensive cancer center

Sally Tan

Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

David Jackman, MD

**Quality & Patient Safety, Thoracic Oncology
Dana-Farber Cancer Institute**

Clinical pathways (CP) is an emerging tool aiming to reduce unwarranted variation and to maximize value in cancer care. CPs that exist today provide real-time, decision-making support for providers, typically for treatment decisions. CPs incorporate individual clinical data to customize a treatment plan within the bounds of evidence-based guidelines and clinical consensus. We describe here the preliminary experiences and challenges of developing and implementing clinical pathways at a comprehensive cancer center.

Dana-Farber Cancer Institute (DFCI) partnered with Via Oncology to develop and pilot a customized CP in lung cancer. This platform tracks usage rate, adherence to the CP (on-pathway rate), and reasons why off-pathway treatments were chosen. Additionally, an online satisfaction survey was conducted among providers participating in the pilot.

Between 1/27/14 and 5/30/14, 277 chemotherapy treatments were initiated, with 124 new patients. CP was used to generate 98% of new chemotherapy orders; 63% were on-pathway. The most common off-pathway reasons were 1) poor patient performance status and 2) treatment beyond 3rd line. 22 of 41 specialists who participated in the CP pilot at DFCI's main campus responded to the survey (54% response rate). Respondents ranked the Institute as the stakeholder who most benefits from CP, followed by payers, DFCI network community physicians, DFCI main campus physicians, and patients. Respondents recognized CP reflects appropriate care but are concerned about workflow. 15 respondents (71%) agreed that this CP reflects an appropriate clinical standard of care, and 14 respondents (64%) agreed that sufficient opportunity was provided to offer input into the pathways design. On the other hand, 19 respondents (86%) disagreed that CP saved them time compared to previous practice.

In conclusion, implementation of an institution-derived CP is feasible at a comprehensive cancer center. Physician input into pathway design is essential to build buy-in, and likely contributed to our high utilization rates. Academic specialists perceived more benefit of CP for their peers practicing in the community and raised concerns about workflow. On-pathway rates at this comprehensive cancer center were lower than those reported in community settings. Ultimately, we envision a much broader role for CP in the future of oncology care. Further iterations of CP could serve as patient-centric platforms providing decision-making support across the continuum of cancer care, and be dynamic enough to accommodate the uncertainty and constantly changing nature of oncology treatment approaches.

Assessment of Breast Cancer Risk Models in U.S. Populations**Anji Tang****Harvard Medical School, HST/London Society, Class of 2018****Peter J Tonellato PhD****Laboratory for Personalized Medicine****Center for Biomedical Informatics****Harvard Medical School**

Although many breast cancer risk prediction algorithms have been developed and discussed in prior literature, systematic testing of multiple algorithms in a large dataset representative of the US is still lacking. Amir et al. conducted one study comparing the accuracy of the Tyrer-Cuzick, BRCAPRO, and Gail models when applied to participants from the Family History Evaluation and Screening Programme in South Manchester. Rosner&Colditz et al. also tested both the Gail model and a clinical version of the Rosner&Colditz model on a cohort from the Nurses Health Study and California Teachers Study. None of these populations were statistically representative of the U.S.

The Breast Cancer Surveillance Consortium (BCSC) consists of survey-based data from over 2 million screening procedures at mammography clinics that covered a wide geographic range and were considered nationally representative. BCSC provided values for common risk factors linked to elevated breast cancer risk in women.

Using BCSC as a reference population, we improved upon earlier studies by generating and testing algorithms on a larger population of clinical avatars, simulated patients generated using an online program called Tetrad. Tetrad uses Bayesian analysis to calculate the conditional probabilities for the breast cancer risk factors and ensure that the statistical distributions for each of the variables are similar in the avatars and real patient population.

In order to generate avatars and fit the risk models, we pre-processed the BCSC data using methods of statistical imputation to fill in missing values and variables. We also adapted the original Rosner&Colditz log incidence model into a computational algorithm written in R, and ran the latest version of the Gail 2012 model using a statistical software called JMP. Then using BCSC-derived clinical avatars, we were able to run multiple simulations of the Gail Model and Rosner&Colditz Model to assess their accuracy with greater sample size and statistical power.

We will evaluate these models by comparing the risks generated for women who developed breast cancer as opposed to women who did not get breast cancer; women who are recorded as having breast cancer should generate much higher risks. We will also characterize the subgroups for which the algorithms generate the most accurate predictions. Our major limitations are the potential errors introduced by the imputation methods and avatar generation, both of which are probability-based simulations. Our results will help us justify running these algorithms as part of clinical routine, or suggest ways to improve their accuracy.

Evaluation of Clinical Tool for Tracking Chemotherapy Completion, Associated Toxicities and Related Adverse Events in Butaro, Rwanda

Kathryn K. Taylor

Harvard Medical School, Francis Weld Peabody Society, Class of 2017

Larry Shulman, MD

Center for Global Cancer Medicine

Dana-Farber Cancer Institute

Cancer is now a leading cause of death and disability in developing countries, yet health systems are largely unable to meet the growing burden. Through innovative partnerships and systems capacity building, high quality cancer care can be delivered even in resource-limited settings, where there are few specialized medical professionals. As part of the collaboration between the Butaro Cancer Center of Excellence (CCOE), Partners in Health (PIH), and Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC), a clinical tracking tool has been implemented to monitor adverse events and toxicities of chemotherapy. Analysis of data assembled by tracking outcomes will guide clinical practice, direct priorities for the program, and promote ongoing quality improvement. Importantly, the clinical tracking tool will provide data for future research. The goal of this study was to assess the effectiveness of the new clinical tracking tool in accurately reflecting chemotherapy associated toxicities and related adverse events data. Data was extracted from the records of all patients admitted for IV chemotherapy from April 8th, when the form was initiated in clinic, through May 31st. The tool was assessed for accuracy in reporting adverse events by comparing data recorded using the tool to clinician's progress notes. Examining completion rate assessed usability. The incidence of adverse events was also evaluated. Within the study period, there were a total of 227 possible charts for abstraction. Of this total, 154 charts were abstracted, 59 were excluded because the patient did not receive IV chemo during study period, and 15 charts were not found. The most common diagnosis of patients included was breast cancer, 52 patients of 154. ALL, HL, NHL were the next most common with 17 patients each. Chemotherapy was administered a total of 392 times, and there were 202 adverse events forms included in the patient records, a completion rate of 51.53%. 78 (38.61%) of these were complete (all fields of the form completed), and 194 (96.04%) forms had 10+ fields completed, out of a possible 13 fields. The most common adverse event was nausea (22.34%), followed by peripheral neuropathy (19.15%), then oral mucositis (12.41%). The most common cause of holding treatment was neutropenia. Further, more in-depth, analysis will be done to evaluate the overall incidence of adverse events, the incidence of adverse events and grades by disease and regimen, comparison of progress notes to form, and the overall use of the form per patient and completeness.

Cellular Mechanisms Underlying Dormant Intestinal Stem Cell Activation**Horatio R. Thomas****Harvard Medical School, Francis Weld Peabody Society, Class of 2017****David T. Breault, MD, PhD****Division of Endocrinology****Boston Children's Hospital**

Two distinct stem cell populations maintain the intestinal epithelium: (1) crypt base columnar (CBC) intestinal stem cells (ISCs) marked by *Lgr5* expression and (2) dormant ISCs (d-ISCs) marked by *mTert* expression. The *Lgr5*⁺ CBC ISCs located at the base of intestinal crypts rapidly cycle and maintain the intestinal epithelium under steady-state conditions. The largely quiescent *mTert*⁺ dormant ISCs located at the “+4” supra-Paneth cell crypt position contribute little under steady-state conditions but play an important role during tissue regeneration following intestinal injury.

In *ad libitum* fed mice, intestinal crypts contain approximately sixteen *Lgr5*⁺ cells, of which 75% are actively cycling. In contrast, crypts contain one *mTert*⁺ cell, on average, of which >90% are quiescent. By comparison, in mice fasted for 48 hours, *Lgr5*⁺ cells show a 50% decrease in cell cycle frequency and a 4-fold increase in apoptosis, while *mTert*⁺ cells show a 10-fold increase in cell number and a 10-fold increase in cell cycle entry (as defined by Ki67⁺, a pan cell cycle marker). While these observations suggest that d-ISCs play a critical role in the response to fasting, it remains unknown whether fasting leads d-ISCs to progress from G₀→G₁, rendering them poised to respond upon re-feeding or whether it results in complete cell cycle progression from G₀→G₁/SG₂M.

To begin to investigate these mechanisms, we studied cell cycle activity during the period immediately preceding the fast and during the period of fasting itself in *Lgr5*-GFP and *mTert*-GFP transgenic mice (n=3 mice per group). Actively cycling cells were marked, *in vivo*, using the DNA labeling agent 5-ethynyl-2'-deoxyurine (EdU) and ISCs (expressing *Lgr5*-GFP or *mTert*-GFP) that co-expressed EdU were quantified in freshly isolated intestinal crypts. Analysis of crypts labeled before the fast revealed few co-positive *mTert*-GFP⁺ EdU⁺ cells (3.8%±0.1%). In contrast, 10-times as many *Lgr5*-GFP⁺ cells were EdU⁺ (41.6%±0.5%). Together, these results confirm that the largely quiescent *mTert*-GFP population is distinct from the actively cycling *Lgr5*-GFP population under steady-state conditions. Ongoing studies will establish the cell cycle status of d-ISCs during fasting, which will provide important insight into the intrinsic cellular mechanisms underlying the regenerative response to physiological stress in the intestine.

Targeting Epigenetic Reprogramming in Glioblastoma Multiforme Cancer Stem Cells with Small Molecules**Rohit Thummalapalli****Harvard Medical School, Irving M. London Society, Class of 2017****Bradley E. Bernstein, MD, PhD****Center for Systems Biology, Massachusetts General Hospital****Angela N. Koehler, PhD****David H. Koch Institute for Integrative Cancer Research at MIT**

Glioblastoma multiforme (GBM) is a devastating malignancy exhibiting a median survival of 13 months, with subpopulations of GBM cancer stem cells (CSCs) responsible for tumor recurrence after chemotherapy. Recent chromatin profiling work has identified a core network of five transcription factors (TFs) responsible for epigenetic reprogramming events critical for tumor propagation, raising the potential for selective targeting of epigenetic circuits in GBM CSCs.

To use high-throughput screening approaches to identify novel inhibitors for two of these TFs, the SOX2 and POU3F2 genes were cloned from a patient-derived GBM-CSC line, with 5' HA tags added by PCR, and overexpressed in CSCs by lentiviral infection. Small molecule microarrays (SMMs) containing 15,000 compounds were printed and run against cellular lysates and purified proteins. Preliminary SMM results against SOX2 protein identified 94 compounds with significant binding intensity ($p < 0.05$) and 18 with $p < 0.01$. For POU3F2, we identified 101 compounds with $p < 0.05$ and 22 with $p < 0.01$. Inconsistent results were observed with the lysate approach, suggesting that optimization of target expression is necessary. Future work involves flow cytometry to validate assay positives by measuring loss of the stemness marker CD133 before ChIP-seq and RNA-seq studies to investigate the mechanism of action of candidate inhibitors.

To identify possible chromatin-modifying enzymes downstream of this TF network as a complementary approach, we tested 21 validated inhibitors of epigenetic regulators for inhibition of CSC proliferation. JQ1, an inhibitor of the epigenetic reader BRD4, exhibited 50 nM IC_{50} in CSCs, with ChIP-seq showing high BRD4 occupancy at enhancers associated with oncogenes, including MYC-N. However, JQ1's significant off-target toxicity (120 nM IC_{50} in human astrocytes) compelled us to explore an alternative avenue for BRD4 inhibition: targeting the arginine demethylase JMJD6 (a known BRD4 functional partner). Co-immunoprecipitation confirmed BRD4/JMJD6 association in GBM CSCs; CRISPR-mediated JMJD6 knockdown experiments are underway.

GSKJ4, an inhibitor of the histone demethylase JMJD3, exhibited 1.8 μ M IC_{50} in CSCs and ten-fold selectivity over its inactive isomer GSKJ5, raising its therapeutic potential. While treatment did not result in significant global increases in H3K27me3 methylation, 1 μ M GSKJ4 significantly decreased proliferation ($p < 0.05$) in a subset of quiescent CSCs marked by high demethylase expression and resistance to dasatinib. Going forward, BRD4 and JMJD3 ChIP-seq experiments in the presence of these inhibitors are planned to further investigate mechanisms of action, while downstream validation of potential SOX2 and POU3F2 probes may help further the discovery of novel therapeutics specifically targeting epigenetic reprogramming in GBM CSCs.

Chromatin Structure in the Aging Brain**Matthew Torre****Harvard Medical School, Walter Bradford Cannon Society, Class of 2015****Mel Feany, MD, PhD****Department of Pathology****Brigham and Women's Hospital**

The elderly (age ≥ 65 years) are one of the fastest growing segments of the population in developed countries, making treatment and prevention of chronic diseases associated with aging even more clinically important. This population is at particular risk of developing dementia. Thus, a better understanding of the pathways underlying brain aging and why certain regions of the brain (e.g. prefrontal cortex and temporal lobe) are more susceptible than others (e.g. occipital cortex) to developing age-related changes is urgently needed.

Epigenetic modifications and the attendant alterations to chromatin structure -- specifically, loss of heterochromatin -- are being increasingly recognized as central mechanisms in aging. We therefore tested the hypothesis that, in elderly patients, neurons in the occipital cortex would have increased heterochromatin compared to neurons in the prefrontal cortex and temporal lobe. Postmortem brains (n=4) from decedents 65-80 years of age were collected through the autopsy service at Brigham and Women's Hospital. The decedents had no clinical history of neurocognitive disorders. Sections of brain from the regions of interest were submitted for microscopic examination, and slides were double-stained for H3K9me2, a histone modification associated with heterochromatin and gene silencing, and NeuN, a neuron-specific marker. By analyzing high magnification images of the stained regions of interest, we were able to calculate the proportion of neurons with positive H3K9me2 chromocenter staining. An additional subset of slides was double stained with NeuN and HP1-alpha, another histone modification associated with heterochromatin.

A lower proportion of neurons within the occipital cortex showed positive staining for H3K9me2 chromocenter staining (5.76%) compared to those in the prefrontal cortex (35.9%, $Z = 8.52$) and in multiple subregions of the temporal lobe, including subiculum (45.8%, $Z = 9.24$), entorhinal cortex (32.7%, $Z = 9.24$), transentorhinal cortex (29.5%, $Z = 6.3$), and CA1, CA2, CA3, and CA4 of the hippocampus (47%, $Z = 9.39$; 45.5%, $Z = 9.66$; 47.4% $Z = 9.31$; and 41.1%, $Z = 7.98$, respectively). Data obtained from HP1-alpha staining were consistent with these findings.

The epigenetic changes associated with brain aging are complex. The reduced heterochromatin staining within the occipital cortex compared to prefrontal cortex and temporal lobe from tissue obtained from elderly decedents is contrary to our initial hypothesis. Further studies should compare how chromatin structure in these regions changes with age (i.e. middle-age versus ≥ 65 years).

Reliability and validity of using hand-held dynamometry and electrical impedance myography to assess hamstring and quadriceps strength in female footballers

Jessica M. Tsao

Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Seward B. Rutkove, MD

Department of Neurology

Beth Israel Deaconess Medical Center

Knee injuries are a serious burden to athletes, compromising not only their athletic career, but also leading to detriments in long-term health through osteoarthritis. Isometric hamstring/quadriceps (H/Q) strength ratio has been implicated as a measurement tool for risk of knee injury, but the gold standard method of measuring muscle strength, isokinetic dynamometry (IKD), lacks portability and ease of use. Hand-held dynamometry (HHD) overcomes these problems and has shown good reliability in some populations, but there is concern that the strength of the tester limits its reliability with stronger muscle groups and individuals. Electrical impedance myography (EIM) has been correlated with muscle strength in individuals with musculoskeletal disease and overcomes the limitations of both IKD and HHD; however, it has not been used as a method of strength measurement in healthy individuals. HHD would allow for widespread use of direct H/Q ratio measurement while EIM could be used as a surrogate measurement. Both HHD and EIM have the potential to permit widespread screening for individuals at risk for knee injury and implement the appropriate intervention. Thus, the purpose of this study was to evaluate the validity of using HHD and EIM and the reliability of HHD to measure H/Q ratio.

Elite female footballers underwent strength testing using IKD (n=21), HHD (n=30), and EIM (n=20). Maximal isometric hamstring and quadriceps strength was measured using HHD and IKD. Maximal isokinetic hamstring and quadriceps strength was also assessed using IKD. Phase, resistance, and reactance of the hamstrings and quadriceps were measured using EIM.

Data collection has been completed and data analysis is still ongoing. Intra-class correlation coefficients and Bland-Altman plots will be used to determine the reliability of the HHD, while Pearson correlation coefficients will be used to determine the relationship of HHD and EIM with gold standard IKD measurements.

**Evaluating the Prognostic Power of a 186-Gene Signature for
Patients with Early Chronic Hepatitis C**

Matthew G. Tung

Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Raymond T. Chung, MD

**Vice Chief, Gastrointestinal Unit & Medical Director, Liver Transplant Unit
Massachusetts General Hospital**

Chronic hepatitis C (CHC) affects over 2% of the world's population and is the leading cause of hepatocellular carcinoma (HCC) as well as the leading indication for liver transplant in the US. CHC eventually leads to declining liver health in patients as normal liver tissue is replaced by inflammation and then fibrotic scar, but the rate at which relatively healthy patients develop serious liver complications is highly variable and relevant to clinical decision-making.

Quantitative prognostic models combining clinical and molecular data are sorely needed, but first candidate genes must be tested in order to identify those with the greatest ability to predict the rate of disease progression. We selected to test a 186-gene signature that has previously been demonstrated to predict outcomes in patients with hepatocellular carcinoma and hepatitis C-related cirrhosis. We aimed to determine whether the signature could be combined with relevant clinical data to predict outcomes for patients earlier in the course of CHC disease progression.

Using the Research Patient Data Registry at Massachusetts General Hospital, we identified a cohort of patients with CHC and index biopsies indicating minimal fibrosis. After matching patients who decompensated rapidly (<12 years after initial biopsy) and slowly (>12 years after initial biopsy without decompensation) on age, race, gender, and alcohol consumption, the cohort included 7 rapid progressors and 19 slow progressors. For each patient, relevant clinical data and laboratory values were collected as well as tissue samples to be analyzed for genotype at the three SNP loci.

Analysis of relevant clinical data confirmed previously reported associations between rate of disease progression and presence of liver steatosis ($p=0.001$) and ALT prior to index biopsy ($p=0.003$). The gene expression is currently being tested, and the results should be obtained within the next few weeks. Once all of the data has been compiled, patients will be classified into high-, intermediate-, and low-risk groups according to the 186-gene signature. We will then determine the odds ratio of rapid decompensation for the intermediate- and high-risk groups relative to the low-risk group in univariate and multivariate models including steatosis and initial ALT. Our results will determine whether the 186-gene signature provides prognostic power not present in currently used laboratory metrics as well as whether such a signature might be useful in the early clinical management of patients with CHC.

Craniofacial Parameters for Optimizing Donor-Recipient Suitability in Face Transplantation**Marvee Turk****Harvard Medical School, Francis Weld Peabody Society, Class of 2017****Bohdan Pomahac, MD****Plastic Surgery Transplantation, Department of Surgery
Brigham & Women's Hospital**

Face transplantation (FT) is increasingly complementing conventional surgical techniques as a treatment option for patients suffering from severe facial deformities. Surgical expertise in FT draws heavily on craniofacial principles derived from important cephalometric and anthropometric parameters. Meticulous attention to different bony and soft tissue landmarks as well as the angles and metrics that define them is critical to ensuring optimal *intra*-operative placement of donor grafts onto corresponding recipient facial structures. The purpose of this study is to leverage the value of these craniofacial principles towards optimizing the *pre*-operative phase of FT donor-recipient matching.

Criteria for the pre-operative matching of donors and recipients is currently based only on age, gender, immune compatibility, and skin color and texture. Optimizing the aesthetic outcomes of the match beyond these basic criteria has yet to occur. As global clinical experience with FT evolves and the availability of facial allograft donors increases, the need for such expanded criteria will increase accordingly. Furthermore, with a trend towards full-face transplants and those of increasing bony complexity, it will be ever more important to incorporate craniofacial principles into the pre-operative matching process.

Previously, a model of virtual face transplantation (VFT) was developed to predict aesthetic outcomes in digitally simulated donors and recipients on the basis of easy-to-measure, pre-operatively acquired craniofacial parameters. This model found donor-recipient mismatch in five soft-tissue and three hard-tissue measurements to be predictive of VFT aesthetic outcome: trichion-to-nasion facial-height, endocanthal width, exocanthal width, mouth-chelion width, subnasale-to-menton facial-height, inner orbit width, palatal-occlusal plane angle, and sellanasion-mandibular plane angle. The goal of the current study is to replicate these predictive measurements in a cohort of *actual* donors and recipients, and thereby determine whether or not the correlation found in VFT applies similarly in actual cases.

At this juncture, available CT angiograms for six FT donors and recipients have been digitized and measured using Dolphin imaging software. Due to obvious limitations in the number of available FT cases, further complicated by challenges in appreciating certain craniofacial parameters in the context of severe disfigurement, additional subjects must be recruited before a sufficiently powered analysis can be completed. As soon as additional FT cases are incorporated, the study will proceed into its next phase, during which aesthetic outcomes for each case will be rated (by independent reviewers) and the extent to which they correlate with the above eight VFT-derived predictive craniofacial parameters will be determined.

Highly Sensitive Troponin I Independently Predicts CRT Non-Response and Clinical Outcome in Cardiac Resynchronization Therapy**Ramkumar V. Venkateswaran****Harvard Medical School, Walter Bradford Cannon Society, Class of 2017****Jagmeet P. Singh, MD, DPhil****Cardiac Arrhythmia Service, Division of Cardiology
Massachusetts General Hospital**

Cardiac resynchronization therapy (CRT) is now a standard treatment for advanced heart failure patients with a wide QRS. However, despite its effectiveness, approximately one-third of patients do not respond to treatment. Recently, more effort has gone into determining predictors of CRT response, including cardiac biomarkers such as troponin.

The objectives of this study were to 1) determine if coronary sinus (CS), peripheral vein (PV), and transcatheter (CS-PV) gradients of high sensitivity troponin I (hsTnI) at the time of device implant were predictive of CRT non-response, 2) determine if changes in biomarker level over 6 months were predictive of CRT non-response, and 3) determine if the addition of hsTnI to an existing model improved risk prediction of CRT non-response.

In 92 patients (65±14 years, LBBB 54%, LVEF 26±8%) treated by the MGH Arrhythmia Service, hsTnI (Siemens Diagnostics) was measured simultaneously in a peripheral vein and the coronary sinus at the time of device implantation. Three study endpoints were measured: 1) HF Clinical Composite Score (a measure of clinical response), 2) left ventricular reverse remodeling (LV-RR defined as >5% improvement in LVEF ≥5%), and 3) two-year MACE (major adverse cardiac events). Multivariable regression analysis accounted for standard predictors of CRT response, including gender, left bundle branch block, and ischemic cardiomyopathy.

Median hsTnI level was 22.8 [interquartile range: 12.2 to 45.1] pg/ml. In univariate analysis, PV hsTnI (log-transformed) was associated with an increased hazard for CRT non-response (OR: 1.8 [1.2–2.7], p=0.01), absence of LV-RR (OR: 1.8 [1.1–2.9], p=0.02), and MACE (HR: 1.6 [1.1–2.3], p=0.01). PV hsTnI remained predictive of CRT non-response (OR: 1.8, p=0.02), absence of LV-RR (OR: 1.7, p=0.03), and MACE (HR: 1.5, p=0.02) following adjustment for baseline covariates. Addition of hsTnI to a model with baseline covariates significantly improved risk prediction of CRT non-response as reflected by net reclassification index analysis (continuous NRI: 0.6 [0.2–1.01], p=0.005). Transcatheter hsTnI, CS hsTnI, and six-month change in PV hsTnI were all not predictive of non-response, LV-RR, or MACE.

In conclusion, peripheral vein hsTnI is predictive of clinical response, LV reverse remodeling, and clinical outcome in patients undergoing CRT. Furthermore, hsTnI incrementally improves risk prediction for CRT non-response. Larger studies need to be done to corroborate the results from this study. More diverse patient populations should also be studied to see if these results can be generalized to patients with less advanced heart failure.

Dr. Vesna Bosanac: Ethical Decisions in Times of War

Ivana Viani

Harvard Medical School, Walter Bradford Cannon Society, Class of 2017
Davis Center for Russian and Eurasian Studies Graduate Research Travel Grant

Harold J. Bursztajn, MD

Department of Psychiatry, Harvard Medical School
Massachusetts Mental Health Center
Mount Auburn Hospital

Sabine Hildebrandt, MD

Boston Children's Hospital, Harvard Medical School
Div. General Pediatrics, Dep. Medicine

Vesna Bosanac, MD (1949-) is a pediatrician who served as the director of a hospital in Eastern Croatia, where in 1991 over 4,000 civilians and soldiers from both defenders' and aggressors' troops sought health care or refuge during the bloodiest battle of the Homeland War (1991-1995). Dr. Bosanac's actions during the war are exemplary of the addition of duties and difficult ethical choices faced by physicians in times of ethnic conflict and war.

Only 32 days in the directorial position at the start of the Battle of Vukovar, Dr. Bosanac faced a dramatic expansion of her professional responsibilities, including coordination of complex logistics concerning the rationing of dwindling supplies of staff, equipment, medications, food, and utilities. Under the immense stress of daily bombardment of the hospital and increasing number of patients from both sides of the conflict, Dr. Bosanac apparently managed to ensure the provision of a surprisingly high level of equitable care, given the circumstances.

This case study elucidates the actions of Dr. Bosanac during the siege of Vukovar and identifies factors that facilitated her ethical decisions under conditions of adversity, catastrophe, and uncertainty. Specifically, the following motivational factors are discussed: Dr. Bosanac's relationships, identifications, memories, values and previous experiences in becoming a physician, and her ability to cultivate these before and during the crisis she had to face.

For this study, we interviewed Dr. Bosanac and ten of her colleagues who worked with her during the war. The study was limited to interviewing persons chosen by Dr. Bosanac, however, we succeeded in interviewing persons of various ethnicity, profession, and length of acquaintance with Dr. Bosanac prior to the war. Historical records and documents were examined in conjunction with the interviews.

We made the preliminary observation that Dr. Bosanac's (1) early exposure to a multi-ethnic population, (2) family education in acceptance of all peoples as fundamentally equal, and (3) instillation of early values which included impeccable work ethic, amiability, resourcefulness, and determination, facilitated her ethical conduct and enabled her to save thousands of lives of her fellow citizens during the most violent armed conflict in Croatia after the Second World War. These factors may serve as starting points for the future examination of qualities needed to be sought and/or developed in those who will be entrusted with the health of populations in times of extraordinary humanitarian crises.

**Using Secure Electronic Messaging via a Patient Portal to Improve Patient Safety
Following Discharge from the Hospital: A Quality Improvement Project**

John Wickman
Harvard Medical School, William Bosworth Castle Society, Class of 2017

Steven Simon, MD, MPH
Chief, Section of General Internal Medicine
Investigator, Center for Healthcare Organization and Implementation Research
VA Boston Healthcare System

Medication discrepancies occur in 3.3 million outpatient visits each year in the United States. The medication discrepancies can lead to adverse events resulting in hospital readmissions and potentially fatal outcomes. The hospital discharge period is a particularly vulnerable time for the patient due to unfamiliarity with changes in their medication regimen, ineffective communication at the time of discharge, the complex nature of readjusting to life at home, and reduced access to a primary care physician. Interventions to reduce discrepancies may reduce readmissions, improve patient satisfaction, and decrease costs of the healthcare system.

Little is known regarding the value of medication reconciliation interventions implemented during the post-discharge period. We therefore undertook a quality improvement project to evaluate the potential effectiveness of a health-information technology tool to improve medication safety following hospital discharge. Veterans were recruited from the inpatient general medical units of the West Roxbury Campus of the VA Boston Healthcare System. Three days following their hospital discharge, Veterans were sent a Secure Messaging Medication Reconciliation Tool (SMMRT) via the Secure Messaging feature of MyHealtheVet (VA online patient portal). The SMMRT contained the patient's medication list, reviewed by a clinical pharmacist, including an image of each medication and the prescribed directions for taking the medication. Veterans completed the SMMRT indicating medication use and returned the tool to our pharmacist. The pharmacist contacted the Veteran directly to follow up on any discrepancies.

We recruited 50 Veterans hospitalized before implementing the SMMRT (i.e., "pre-intervention") and 50 after implementation (i.e., "post-intervention"). We assessed medication discrepancies and hospital utilization (emergency room visits and readmissions) thirty days after discharge, using a combination of telephone interview and chart review, for both pre- and post-intervention participants. Among the 50 pre-intervention participants, we identified medication discrepancies among 38 of 42 Veterans (90%) we reached for follow up. A total of 8 Veterans (16%) had evidence of readmission or emergency department utilization within 30 days of discharge. Follow up of the post-intervention participants is ongoing; thus far, we have reached a total of 32 of the 50 enrolled post-intervention participants, among whom 28% had medication discrepancies and 18.8% had evidence of readmission or ED utilization.

These data suggest the SMMRT intervention may significantly decrease the risk of medication discrepancies in the post discharge period. The results to date do not indicate a reduction in the risk of hospital readmission or ED utilization for Veterans utilizing the SMMRT intervention. The study was limited by the pre-post design and the small number of participants, as well as incomplete follow-up. However, lessons learned from the process of patient recruitment and follow-up will help to guide a future randomized controlled trial of the SMMRT intervention. Moreover, future refinements will consider the possibility that SMMRT alone may not suffice to reduce hospital utilization and that additional elements may need to be added to the intervention.

Provider-Level Barriers to Uptake of Uterine Balloon Tamponade for Management of Post-Partum Hemorrhage in Freetown, Sierra Leone

Anne Marie Williams
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Roy Ahn, ScD
Division of Global Health and Human Rights
Department of Emergency Medicine
Massachusetts General Hospital

Post-partum hemorrhage (PPH) is a leading cause of maternal mortality worldwide, and a significant problem in Sierra Leone, where 890 maternal deaths per 100,000 live births represents the 4th highest maternal mortality rate in the world. Women in low-resource settings such as Sierra Leone, whose health system was severely weakened during the 1991-2002 civil war, are at high risk of morbidity and mortality due to PPH. However, even in low-resource settings, death from PPH can be avoided through proper management.

Uterine balloon tamponade is one such management tool, which consists of the insertion and inflation of a balloon into the uterine cavity to achieve a tamponade effect. A low-cost balloon can be constructed from a condom, catheter and string. Stemming from successful work training providers in South Sudan and Kenya in PPH management with UBT, we are conducting a multi-center trial in health centers in Freetown, Sierra Leone. The objective of the study is to evaluate the effectiveness, safety, and uptake of UBT in managing uncontrolled PPH, and to identify provider-level barriers to effective UBT use.

Since December 2013, our team has trained providers from over one hundred health facilities around Freetown in PPH management incorporating UBT. Through active field-based surveillance we collected longitudinal quantitative data on UBT use at these facilities, and performed semi-structured follow-up interviews with providers who have used the balloon. I followed up on cases that took place during the time I was in Sierra Leone, and will be coding and analyzing the entire set of interviews with two other researchers. Coding and analysis of interviews is in progress. We are employing both an inductive and deductive coding approach to derive analytical themes from our data.

Because UBT is intended for use alongside many other interventions in an emergency setting to manage PPH, it can be difficult to isolate the life-saving impact of UBT. This limitation is compounded by the lack of historical data in the resource-poor settings where our work is based. Our study attempts to address this limitation by focusing on the safe and effective use of UBT in the context of the entire PPH management pathway.

Preliminary data suggest that trained providers are safely and effectively utilizing UBT to manage uncontrolled PPH. Emerging themes suggest that supply shortages, systemic challenges, and training and comprehension of providers represent the main challenges, and present opportunities for improving implementation in this setting and in the future.

A Formative Assessment of a Pediatric Development Clinic in Rwinkwavu, Rwanda**Nina A. Woolley****Harvard Medical School, William Bosworth Castle Society, Class of 2017****Kim Wilson, MD, MPH****Associate Director, Center for Global Pediatrics****Boston Children's Hospital**

With improvements in hospital-based neonatal care in Rwanda, more low birth weight, preterm, and critically ill infants are surviving the neonatal period. After discharge from special care nurseries, these children are at high risk for poor growth and neurodevelopment outcomes. In partnership with the Rwanda Ministry of Health, Partners In Health/Inshuti Mu Buzima launched a Pediatric Development Clinic (PDC) in April 2014 to target these children with services.

The PDC aims to provide integrated management of the medical, nutritional, and developmental needs of high-risk children, aged 0-5, and introduce early childhood development activities into the continuum of healthcare. Enrolled patients include those with prematurity, low birth weight, birth asphyxia or other perinatal complications, suspected genetic syndromes, and neurodevelopmental disability. The PDC is the first program of its kind in Rwanda. As such, early assessment is critical for ongoing decisions about its implementation and expansion.

We conducted a mixed-methods quality-improvement assessment to evaluate the first four months of PDC operations, April-July 2014. We conducted a chart review to describe patient characteristics and assess initial protocol adherence. We held 3 focus groups with a total of 24 caregivers of patients to assess the acceptability, accessibility, and perceived value of the clinic. We also interviewed all PDC staff to assess acceptability, self-assessed competency, and perceived value of the clinic.

In its first four months, the PDC enrolled 77 patients. The most common reason for referral was prematurity/low birth weight (37.7%), followed by hypoxic ischemic encephalopathy (31.1%). The average birth weight among premature/low birth weight infants was 1575 grams (3.47 lbs). Providers are delivering most services according to protocol. Despite successful completion of training with pre/post test improvement, however, providers need additional training in certain tasks such as plotting growth charts and assessing patient neurodevelopment.

Focus group discussions reveal that caregivers greatly value the PDC. One key value of PDC is the provision of peer-to-peer support, which is consistent with literature documenting the positive impact of mothers groups. However, the caregivers face barriers to coming to the clinic, chiefly opposition from husbands, transportation costs, and stigma from neighbors. Caregivers would like home visits for family counseling and expansion of PDC to new sites.

The assessment suggests that the PDC is filling an important need in the community and reveals key ways to improve the clinic during its next stage of operation.

Identifying factors associated with smoking cessation after hospital discharge**Mark Wu****Harvard Medical School, Francis Weld Peabody Society, Class of 2017****Nancy A. Rigotti, MD****General Medicine Division****Massachusetts General Hospital**

Hospitalization provides an opportune moment to promote smoking cessation for millions of smokers each year. Despite the advantages provided by the inpatient setting for helping patients quit, a significant number resume smoking after discharge. We aimed to identify the predictors of smoking cessation at 6 months post-discharge among hospitalized patients. We hypothesized that less nicotine dependence, being admitted with smoking related diagnosis, and greater confidence quitting would be associated with increased smoking cessation at 6 months.

This was a secondary analysis of prospectively-collected data from the Helping HAND randomized controlled trial (JAMA 2014; 312:719-728). Smoking history, baseline demographic information, and smoking status at 6 months were collected for all 397 participants. The primary outcome was biochemically-validated past 7-day point prevalence tobacco abstinence 6 months after discharge. We conducted bivariate analyses to explore the relationship between covariates and the outcome measure. Chi-squared tests were used to assess statistical significance for categorical variables and student t-test for continuous variables. Covariates with a $p \leq .05$ were entered into a multiple logistic regression model that adjusted for study group. Odds ratios (OR) and 95% confidence intervals (CI) calculated were used to assess statistical significance.

There were 397 study participants analyzed. Their mean age was 53 years, 48% were male, 81% were non-Hispanic whites, and 51% had a high school education or less. The 6-month quit rate was 22%. Age, gender, race, FTND (measure of nicotine dependence), confidence quitting, smoking-related discharge diagnosis, and study group were included in the multiple logistic regression model. Smoking cessation at 6 months was more likely in patients who were older (mean 55.8 vs. 51.7, OR: 1.03, CI:1.002-1.055), had a smoking-related discharge diagnosis (29.6% vs. 12.8%, OR: 2.31, CI:1.27-4.2), were male (25.9% vs. 15.2%, OR: 2.27, CI:1.3-4.0), were non-white (24.0% vs. 19.6%, OR: 2.06, CI:1.03-4.1), had a lower FTND score (mean 4.1 vs. 4.9, OR 0.84, CI: 0.74-0.96 per point) and were in the intervention arm (25.8% vs. 15.1%, OR: 2.09, CI: 1.18-3.70) were more likely to quit at six months.

The analysis confirmed our hypotheses that post-discharge smoking cessation would be associated with less nicotine dependence, having a smoking related disease causing the hospitalization, and greater confidence to quit. Characterizing patients more or less likely to quit will provide a good foundation for understanding the barriers to quitting. It may also lead to more directed and effective cessation programs by targeting those who will benefit most from hospital-based smoking interventions.

Factors Influencing Antiretroviral Treatment Adherence among Perinatally HIV-Infected Adolescents in Thailand**Luyi Xu****Harvard Medical School, Walter Bradford Cannon Society, Class of 2017****Gender Trends in Obstetrics and Gynecology Department-based Leadership Roles across ACOG Districts
Thai Studies Fund****Sophie Le Coeur, MD, PhD****Director of Research, Program for HIV Prevention and Treatment****Kerim Munir, MD, MPH, DSc****Developmental Medicine Center, Division of Developmental Medicine
Boston Children's Hospital**

With increasing effectiveness and availability of antiretroviral therapy (ART), perinatally infected children are emerging as the new faces of the global HIV/AIDS pandemic. As of 2013, Thailand has achieved an estimated 57-68% ART coverage among children aged 0-14 years according to UNAIDS. However, studies have suggested decreased adherence and rebound in mortality in adolescents receiving ART.

This study used a mixed-method approach to characterize the patterns of nonadherence and identify factors influencing adherence among perinatally infected adolescents in Thailand. We performed multivariate analysis of data from Teens Living With Antiretrovirals (TEEWA) study, a cross-sectional survey of 709 perinatally HIV-infected adolescents (aged 11-19) and their caregivers throughout Thailand in 2010-2012. We also conducted 12 qualitative interviews with infected adolescents or their caregivers in Chiangmai Province to further elicit in-depth experiences of living with HIV and challenges in adhering to ART.

Initial statistical analysis restricted to the 573 adolescents living in family setting showed that longer treatment duration (≥ 7 years), nondisclosure to the child, death of one or both parents, poor relationship with caregiver(s) and/or health providers, and lower degree of happiness were significantly associated with nonadherence. Behaviorally, having a boy/girlfriend, getting drunk, playing computer games and chatting on the Internet were also strong contributors. Similarly, preliminary findings from the in-depth interviews suggested that tiredness of long-term treatment, forgetfulness due to various activities, and fear of disclosing HIV status to others, especially boy/girlfriends, were important factors of nonadherence. Poor relationship with the caregiver(s), ill-planned disclosure of HIV status to the child, and unpleasant experiences with ART also negatively influenced adherence. Mental support and counseling from peer group was consistently reported as a strong positive factor to encourage adherence. Next analyses will involve refining the multivariate model, and identifying specific themes from the qualitative interviews.

The study is limited by several factors. In the TEEWA study, to prevent unintended disclosure of HIV status to the adolescents, some variables related to adherence could not be measured or were only indirectly assessed via the adolescent's caregiver. In-depth interview participants were recruited through good connection with support organizations and were not intended to be representative of infected adolescents at large, but to provide a qualitative dimension to understand treatment adherence. A mixed-method design helps to compensate the limitations in each approach. These data highlight unique challenges in ART adherence during the transitioning period of adolescence, and suggest addressing interpersonal relationships and psychosocial factors in future interventions.

Examining associations between the expression of HLA class I molecules and the neoantigen burden

David D. Yang

Harvard Medical School, Irving M. London Society, Class of 2017

Matthew L. Meyerson, M.D., Ph.D.

Professor of Pathology

Dana-Farber Cancer Institute and Harvard Medical School

The mechanisms that allow tumors to evade the immune system are not well-understood. Cells in the body are under surveillance via antigenic peptides presented through Major Histocompatibility Complex (MHC) class I molecules, composed of the heavy chain, encoded by the 3 highly polymorphic Human Leukocyte Antigen (HLA) class I loci, non-covalently bound to the β 2-microglobulin (β 2m). Typically, neoantigens expressed on virally infected cells or tumor cells are recognized by cytotoxic T lymphocytes, causing the offending cells to be destroyed. The peptide-presentation profiles of the >6500 documented variants that make up the 3 HLA class I loci vary between one another. Therefore, I predict that HLA class I alleles demonstrate a higher degree of allele-biased expression in tumor samples compared to normal samples for lung squamous cell carcinoma; specifically, I hypothesize that alleles predicted to present neoantigens would be downregulated.

Allelic-specific expression (ASE) of HLA class I molecules in 350 tumors and 36 normal samples will be quantified using mRNA sequencing. The germline HLA class I allelic genotype will be determined from whole-exome sequencing data. Next, mRNA sequencing reads will be aligned to the germline HLA class I alleles' coding sequence to calculate the ASE. The neoantigen burden will be quantified by counting the number of mutations that are computationally predicted to result in a neoantigen that gets presented by one of the 6 different MHC class I complexes. Finally, a generalized linear model will be used to examine associations between HLA class I ASE and the neoantigen burden.

Results show that for paired normal samples, there is balance in allelic expression at all 3 HLA class I loci. However, a subset of the 36 corresponding paired tumors exhibits allelic imbalance for at least one locus. A similar proportion of the 314 unpaired tumors exhibits allelic imbalance for at least one locus. The next steps will be to determine the neoantigen burden and model the association between HLA class I ASE and the neoantigen burden.

This project may present a look into a novel mechanism for immunoevasion. If tumors indeed downregulate certain HLA class I molecules to evade detection, upregulating HLA class I expression may be a possible target for future immunotherapy. However, due to the high degree of homology among HLA class I alleles and the short sequencing read length (50 bp), many fragments and/or reads cannot be used to differentiate between alleles, resulting in an underestimation of the true ASE.

**The Association between Subcutaneous Fat Fibrosis
and the Propensity to Store Fat Viscerally**

Aaron J. Yeoh

Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Caroline S. Fox, MD, MPH

Senior Investigator, Framingham Heart Study,

National Heart, Lung, and Blood Institute

Associate Clinical Professor of Medicine, Harvard Medical School

Background: Alterations in the cellular characteristics of subcutaneous adipose tissue (SAT) may reduce its ability to expand in times of caloric excess, increasing the propensity to store excess calories viscerally (VAT). We hypothesized that increased SAT density, an indirect marker of fat quality, would be associated with 1) an increased VAT/SAT ratio and increased CVD risk and 2) that these associations would be independent of the absolute volume of SAT.

Methods: We investigated the association of SAT density with VAT/SAT ratio and CVD risk in 3212 participants (47.5% women, mean age 50.7 years) from the Framingham Heart Study. Adipose tissue depot density and volume were quantified by computed tomography; traditional cardiovascular disease (CVD) risk factors were quantified.

Results: Higher SAT density was correlated with higher VAT/SAT ratio in men ($r = 0.17$; $p < 0.0001$) but not in women ($r = 0.04$; $p = 0.05$). More adverse levels of CVD risk factors were observed in the high SAT density/high VAT/SAT ratio group compared with the referent group (low density/low ratio). For example, women had an increased risk of diabetes (odds ratio [OR]: 6.7; 95% CI: 2.7-17.6; $p = 0.0001$) and hypertension (OR: 1.6; 95% CI: 1.7-2.4; $p = 0.009$). Additional adjustment for SAT volume generally strengthened these associations (diabetes OR: 10.8; 95% CI: 4.1-29.0; hypertension OR: 2.5; 95% CI: 1.7-3.7; all $p < 0.0001$). These trends were similar but generally weaker in men.

Conclusion: High fat density, an indirect marker of fat quality, is associated with the propensity to store fat viscerally vs. subcutaneously, and jointly characterized by an increased burden of CVD risk factors.

Limitations: The cross-sectional design limits inferences of temporality and the observational nature of the data prevents causality to be concluded from our results. Our cohort is primarily non-Hispanic white, which may limit the generalizability of our findings.

Pancreatic Neuroendocrine Tumors: Surgery vs. Surveillance**Irene Y. Zhang****Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017****Cristina R. Ferrone, MD****Division of General and Gastrointestinal Surgery, Department of Surgery,
Massachusetts General Hospital**

Pancreatic neuroendocrine tumors (PNETs) represent approximately 3% of primary pancreatic neoplasms, with approximately 1000 new cases per year in the United States. Currently, few therapeutic options exist, with surgical resection being the only curative treatment. However, despite improvements in surgical outcomes, pancreatic operations continue to be risky, with over 40% of patients experiencing complications. Therefore, it is critical to understand for which patients surgical resection offers therapeutic benefit, a key question that has not yet been resolved.

To investigate this, a retrospective cohort study was conducted to compare the outcomes of PNET patients who underwent surgical resection and those who underwent surveillance. In particular, this study aimed to identify clinicopathologic factors predictive of favorable operative and non-operative courses, and ultimately to analyze the independent effect of surgery on metastasis and survival. Data were collected by retrospective chart review on all adult patients diagnosed with a benign or malignant neoplasm of the islets of Langerhans, who presented to Massachusetts General Hospital between January 1, 1998 and March 31, 2014, and who had at least one radiologic follow-up available. Potential prognostic factors examined included age, gender, race, tumor size, tumor growth rate, tumor functional status, distant organ metastasis, pathological TNM stage, mitotic activity, Ki-67 proliferative index, WHO grade, surgical complications, and the Charlson Comorbidity Index (CCI) at baseline.

A total of 288 patients were analyzed, including 235 operative and 53 non-operative patients. Overall, the operative cohort had a significantly longer survival than the non-operative cohort ($p < 0.0001$), with 78.9% of operative patients surviving at ten years, compared to 42.7% of non-operative patients. In multivariate analysis, metastasis was the only significant predictor of overall survival for the non-operative cohort ($p = 0.0042$), as well as for the operative cohort ($p < 0.0001$). In predicting the time to metastasis, tumor size at diagnosis was significant in the non-operative cohort ($p = 0.0137$), while CCI ($p = 0.0098$), race ($p = 0.0095$), and Ki-67 ($p = 0.0002$) were significant in the operative cohort. Ultimately, an operation ($p = 0.005$) was a significant prognostic factor for overall survival after controlling for metastases. However, an operation was not a significant prognostic factor for time to metastasis after controlling for race and CCI.

These data suggest that surgical resection of PNETs may offer an advantage in overall survival for patients, though resection does not appear to delay distant metastasis. Additional studies will be needed to validate these findings among a larger and broader patient population.

Association of Androgen Deprivation Therapy with Excess Cardiac-Specific Mortality in Men with Prostate Cancer

David R. Ziehr

Harvard Medical School, Walter Bradford Cannon Society, Class of 2015

Paul L. Nguyen, MD

Department of Radiation Oncology

Dana-Farber Cancer Institute and Brigham and Women's Hospital

Androgen deprivation therapy (ADT) is a mainstay of prostate cancer therapy. As an adjuvant to definitive radiotherapy, ADT has been shown to improve prostate cancer survival in men with locally advanced or localized, unfavorable-risk disease. However, ADT has been associated with increased risk of incident diabetes mellitus, coronary artery disease, and myocardial infarction (MI). Moreover, receipt of ADT may lead to increased all-cause mortality in men with prostate cancer and preexisting cardiovascular comorbidity.

The purpose of this project was to determine if ADT is associated with excess cardiac-specific mortality (CSM) in men with prostate cancer and no cardiovascular comorbidity, coronary artery disease risk factors, or congestive heart failure (CHF) or past MI.

In all, 5077 men (median age, 69.5 years) with cT1c-T3N0M0 prostate cancer were treated with brachytherapy with or without neoadjuvant ADT (median duration, four months) between 1997 and 2006. Fine and Gray's competing risks analysis evaluated the association of ADT with CSM, adjusting for age, year of brachytherapy, and ADT treatment propensity score among men in groups defined by cardiac comorbidity.

After a median follow-up of 4.8 years, no association was detected between ADT and CSM in men with no cardiac risk factors (1.08% at 5 years for ADT vs 1.27% at five years for no ADT, adjusted hazard ratio (AHR) 0.83; 95% confidence interval (CI), 0.39-1.78; $P=0.64$; $n=2653$) or in men with diabetes mellitus, hypertension, or hypercholesterolemia (2.09% vs 1.97%, AHR, 1.33; 95% CI, 0.70-2.53; $P=0.39$; $n=2168$). However, ADT was associated with significantly increased CSM in men with CHF or MI (AHR 3.28; 95% CI 1.01-10.64; $P=0.048$; $n=256$). In this subgroup, the five-year cumulative incidence of CSM was 7.01% (95% CI 2.82-13.82%) for ADT vs 2.01% (95% CI 0.38-6.45%) for no ADT.

In conclusion, ADT was associated with a five percent absolute excess risk of CSM at five years in men with CHF or prior MI, suggesting that administering ADT to 20 men in this potentially vulnerable subgroup could result in one cardiac death. While this study would benefit from longer follow-up as well as a cohort drawn from several, instead of one, institution, its results encourage clinicians to consider the heart health of their patients when appraising the benefits of ADT for the treatment of prostate cancer.