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 support of the annual Soma Weiss Student Research Day.
Soma Weiss
1899-1942
Faculty Committee for Scholarship in Medicine

Jeffrey N. Katz, MD, Faculty Director
Patricia D’Amore, PhD, Chair
Raymond Chung, MD
John G. Flanagan, PhD
Jennifer Haas, MD, MPH
Elizabeth Klerman, MD, PhD
Jeffrey A. Linder, MD, MPH, FACP
Joseph Majzoub, MD
Richard Mitchell, MD, PhD
Janet Mullington, PhD
Kerim Munir, ScD, MBBS
Dan Palazuelos, MD, MPH
Shiv Pillai, MD, PhD
Stephanie Seminara, MD

Advisory Committees in Scholarship in Medicine

Global and Community Health Advisory Committee

Global Health
Jen Kasper, MD, MPH (Co-Chair)
MaryCatherine Arbour, MD, MPH
David Bangsberg, MD, MPH
Ingrid Bassett, MD, MPH
Myron Belfer, MD, MPA
Hilario Cranmer, MD, MPH
David Golan, PhD, MD
Franklin Huang, MD, PHD
Rebecca Luckett, MD, MPH
Kerim Munir, ScD, MBBS
Kristian Olson, MD, MPH, DTMH
Dan Palazuelos, MD, MPH
Guiseppe Raviola, MD, MPH
Dennis Ross-Degnan, ScD
Christian Russ, MD, DTMH
Edward Ryan, MD, DTMH
Juliana Schantz-Dunn, MD
Brittany Seymour, DDS, MPH
Kim Wilson, MD, MPH
Blair Wylie MD, MPH

Community Health
Bobby Gottlieb, MD, MPH (Co-Chair)
Ayse Atasoylu, MD
Jeffrey Collins, PhD, MD
Dharma Cortes, PhD
Justeen Hyde, PhD
Gil Noam, PhD, EdD
Jim O’Connell, MD
Joel Sawady, MD
Health Policy / Health Services Advisory Committee
Lisa Iezzoni, MD, MSc (Chair)
Nancy Keating, MD
Danny McCormick, MD
Jonathan Winickoff, MD

Medical Humanities Advisory Committee
Scott Podolsky, MD (Chair)
Rafael Campo, MA, MD
Joel Katz, MD
Martha Montello, PhD
Amy Ship, MD
Amy Sullivan, EdD
Robert Truog, MD

Outcomes Research / Quality Improvement / Clinical Epidemiology
Advisory Committee
Emma Eggleston, MD (Chair)
Karen Costenbader, MD, MPH
Michele R. Hacker, ScD
Shoshana Herzig, MD
Bobby Yeh, MD

Systems Innovation in Primary Care Advisory Committee
Barbara Ogur, MD (Chair)
Rushika Fernandopulle, MD, MPP
Holly Oh, MD
Steven Simon, MD
Erin Sullivan, PhD
Soma Weiss Student Research Day
January 12, 2016

HARVARD MEDICAL SCHOOL

76TH ANNUAL
Soma Weiss Student Research Day
January 12, 2016

Poster Sessions
2:00 - 4:00 PM
Atrium of the Tosteson Medical Education Center
260 Longwood Avenue, Boston, Massachusetts

Student Presentations and Poster Awards
4:15 - 5:15 PM, Room 209, Tosteson Medical Education Center

Welcome
Edward Hundert, MD, Dean of the Faculty of Medicine and Caroline Shields Walker Professor of Medicine at Harvard Medical School

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
Amir Ameri (Peabody Society) - Survival Roles for RagA and RagB in Acute Myeloid and T-Cell Acute Lymphoblastic Leukemias
Jonathan Fischer (London Society) - Simultaneous Mutation Detection and RNA-Seq in Single Cancer Cells
Margaret Krasne (Castle Society) - Barriers to Uptake of WHO Safe Childbirth Checklist in Five Intervention Health Facilities in Phase II of the BetterBirth Trial: A Quantitative and Qualitative Analysis
Winona Wu (Holmes Society) - The Role of Intermittent Hypoxia in Pathogenesis of Non-Alcoholic Fatty Liver Disease

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
Leon Eisenberg Prize for Medicine in Society Research
## Table of Contents

**Current Year 2 Students**

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mohammad Abbasi</td>
<td>Clinical and Genetic Investigation of Patients with Recurrent Arterial Dissections</td>
<td>2</td>
</tr>
<tr>
<td>Nora Abo-Sido</td>
<td>A Qualitative Exploration of Community Health Work in Lebanon</td>
<td>3</td>
</tr>
<tr>
<td>Michael Alcalá</td>
<td>Listening for a Patient’s Story: Identifying Themes of the Patient-Doctor Relationship through Narrative Patient Interviews</td>
<td>4</td>
</tr>
<tr>
<td>Amir Ameri</td>
<td>Survival Roles for RagA and RagB in Acute Myeloid and T-Cell Acute Lymphoblastic Leukemias</td>
<td>5</td>
</tr>
<tr>
<td>Annabelle Anandappa</td>
<td>Establishing a pipeline to discover the T cell repertoire after neoantigen vaccine using paired TCRαβ chain single cell sequencing</td>
<td>6</td>
</tr>
<tr>
<td>Jordan Anderson</td>
<td>Analysis of variation over time in bundled payment costs</td>
<td>7</td>
</tr>
<tr>
<td>Aditya Ashok</td>
<td>An Analysis of Modern Priorities in Medical Education</td>
<td>8</td>
</tr>
<tr>
<td>Soraya Azzawi</td>
<td>A Systematic Review of National Policies on Tuberculosis Contact Investigations</td>
<td>9</td>
</tr>
<tr>
<td>Lauren Azzopardi</td>
<td>Trends in Orthognathic Surgery</td>
<td>10</td>
</tr>
<tr>
<td>Francesca Barrett</td>
<td>Implementing E-Visits in Partners Primary Care Practices</td>
<td>11</td>
</tr>
<tr>
<td>Melanie Baskind</td>
<td>Culturally Tailored Cooking and Nutrition Skills Workshops for Haitians in the Cambridge Area</td>
<td>12</td>
</tr>
<tr>
<td>Seth Bradbury</td>
<td>The role of Vascular Endothelial Growth Factor in intramembranous ossification during embryonic mandibular development</td>
<td>13</td>
</tr>
<tr>
<td>Eileen Brandes</td>
<td>High-Value, Cost-Conscious Care in Medical Education</td>
<td>14</td>
</tr>
<tr>
<td>Kyle Burton</td>
<td>The Yield of Subsequent Radiographs During Nonoperative Treatment of Radial Head and Neck Fractures</td>
<td>15</td>
</tr>
<tr>
<td>Kia Byrd</td>
<td>Depression and Previous Malnutrition as Predictors of Breastfeeding Duration</td>
<td>16</td>
</tr>
<tr>
<td>Christopher Calahan</td>
<td>Understanding Links between Childhood Adversity and Midlife Health Outcomes: A Longitudinal Study Across Generations</td>
<td>17</td>
</tr>
<tr>
<td>Severine Cao</td>
<td>A prospective study of circulating anti-HLA antibodies in lung transplantation</td>
<td>18</td>
</tr>
<tr>
<td>Emmanuel Carrodeguas</td>
<td>Quantifying the gender difference in radiation risk from lung cancer screening and follow-up: A mathematical modeling</td>
<td>19</td>
</tr>
<tr>
<td>Study Title</td>
<td>Author(s)</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Study of Imaging Patterns Predict Survival in Recurrent Glioblastoma Patients Treated With Bevacizumab</td>
<td>Ken Chang</td>
<td></td>
</tr>
<tr>
<td>Barriers to Accessing Care: Understanding Nonattendance Among Spanish-Speaking Patients</td>
<td>Carolina Chiou</td>
<td></td>
</tr>
<tr>
<td>Evaluating the Implementation and Management of a Task-Sharing Strategy for the Integration of Mental Health and HIV/AIDS Care in Tanzania</td>
<td>Stephanie Choi</td>
<td></td>
</tr>
<tr>
<td>Deficits of Language, Speech and Writing in Idiopathic Normal Pressure Hydrocephalus</td>
<td>Esther Chung</td>
<td></td>
</tr>
<tr>
<td>Mapping Childhood Malnutrition in Chiapas, Mexico</td>
<td>Maggie Cochran</td>
<td></td>
</tr>
<tr>
<td>Characterizing the interactions of Bcl11a and mammalian SWI/SNF (BAF) chromatin remodeling complexes</td>
<td>Dawn Comstock</td>
<td></td>
</tr>
<tr>
<td>Examining the Value of MRI in the Initial Management of Patients with Suspected Rotator Cuff Tears</td>
<td>Alejandro Cortes</td>
<td></td>
</tr>
<tr>
<td>Clinical features associated with aggressive phenotype among immunohistochemically confirmed atypical adenomas</td>
<td>David James Cote</td>
<td></td>
</tr>
<tr>
<td>Stability of High-Quality Warfarin Anticoagulation in a Community-Based Atrial Fibrillation Cohort: The ATRIA Study</td>
<td>Liane Dallalzadeh</td>
<td></td>
</tr>
<tr>
<td>Development of a Smart-Phone based Application to Estimate Repolarization Alternans</td>
<td>Steven Dalvin</td>
<td></td>
</tr>
<tr>
<td>Effect of Social Media on Dissemination of Preventive Oral Health Measures Through Accessible Online Learning Modules in Rwanda</td>
<td>Lindsay D'Amato</td>
<td></td>
</tr>
<tr>
<td>Use of Oblique Back-illumination Microscopy to image cellular interactions through Blood Flow</td>
<td>Paul Dannenberg</td>
<td></td>
</tr>
<tr>
<td>Tube Thoracostomy for Traumatic Hemothorax: Are We Too Eager to Intervene?</td>
<td>Leah Demetri</td>
<td></td>
</tr>
<tr>
<td>Postoperative Pain Management among Dominican and American Health Care Providers: A Qualitative Analysis</td>
<td>Christopher Devine</td>
<td></td>
</tr>
<tr>
<td>Population-Level Evidence for an</td>
<td>Ryan Din</td>
<td></td>
</tr>
</tbody>
</table>
Association between Pulmonary Hypertension and Diabetes

**Alyssa Ehrlich**
Discovering Circular RNAs in Dopamine Neurons of Human Brain: Implications for Parkinson’s Disease

Temporal Trends and Comparative Effectiveness of Bivalirudin versus Unfractionated Heparin for Percutaneous Coronary Intervention among Patients with Acute Myocardial Infarction: A Report From the National Cardiovascular Data Registry

**Enrico Ferro**
Discovering Circular RNAs in Dopamine Neurons of Human Brain: Implications for Parkinson’s Disease

Simultaneous Mutation Detection and RNA-Seq in Single Cancer Cells

**Jonathan Fisher**
Simultaneous Mutation Detection and RNA-Seq in Single Cancer Cells

Quality of End-of-Life Care for the Myelodysplastic Syndromes: Findings from a Large National Database

**Sean Fletcher**
Simultaneous Mutation Detection and RNA-Seq in Single Cancer Cells

When do women decide to undergo sterilization? A qualitative study to evaluate the utility of the federally-mandated Medicaid waiting period

**Olivia Foley**
Simultaneous Mutation Detection and RNA-Seq in Single Cancer Cells

Heart Failure Outcomes in Stable Patients with Prior Atherothrombosis: Observations from the TRA 2°P-TIMI 50 Trial

**Benjamin Freedman**
Heart Failure Outcomes in Stable Patients with Prior Atherothrombosis: Observations from the TRA 2°P-TIMI 50 Trial

Role of Piezo2 in zebrafish muscle and craniofacial development

**Laurel Fuentes**
Role of Piezo2 in zebrafish muscle and craniofacial development

The Effect of Point-of-Care Price Information on Outpatient Pediatric Physician Ordering Behavior

**Smitha Ganeshan**
The Effect of Point-of-Care Price Information on Outpatient Pediatric Physician Ordering Behavior

Analysis of outcomes, complications, and direct costs in patient undergoing lobectomy for stage I lung cancer

**Abraham Geller**
Analysis of outcomes, complications, and direct costs in patient undergoing lobectomy for stage I lung cancer

Involving “Persons with Patient Experiences” in Healthcare Quality Improvement and Redesign: Lessons from Region Jönköping County, Sweden

**Galina Gheihman**
Involving “Persons with Patient Experiences” in Healthcare Quality Improvement and Redesign: Lessons from Region Jönköping County, Sweden

Improving the Versatility of Genome Editing: Screening and Characterizing Cas9 Orthologues

**Jingyi Gong**
Improving the Versatility of Genome Editing: Screening and Characterizing Cas9 Orthologues

Modeling Hypnotic Overuse in Insomniacs

**Frank Gonzalez**
Modeling Hypnotic Overuse in Insomniacs

Retrospective Analysis of Arthroscopic Surgery (lysis and lavage): Relationship between Clinical Presentation, Comorbidities, and Outcomes.

**Gabriel Grisham**
Retrospective Analysis of Arthroscopic Surgery (lysis and lavage): Relationship between Clinical Presentation, Comorbidities, and Outcomes.

Correlating Gait Variability after Increased Cognitive Load with Brain Volume and Cortico-spinal Myelin Content in Cognitively intact Parkinson’s disease Patients: A Pilot Study

**Ricardo Guerra**
Correlating Gait Variability after Increased Cognitive Load with Brain Volume and Cortico-spinal Myelin Content in Cognitively intact Parkinson’s disease Patients: A Pilot Study
<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catherine Gutierrez</td>
<td>Analysis of State Policies and their effects on Freestanding Emergency Departments</td>
<td>50</td>
</tr>
<tr>
<td>Anand Habib</td>
<td>Examining Loss to Follow-Up in an Outpatient Under-nutrition Treatment Program in Saint Nicholas Hospital (Haiti): Implications for Improvement</td>
<td>51</td>
</tr>
<tr>
<td>Tyler Haeffs</td>
<td>Assessment of Provider Nonverbal Communication and the Patient-Doctor Relationship within Various Health Settings</td>
<td>52</td>
</tr>
<tr>
<td>Kelsey Han</td>
<td>Developing and evaluating a surgical iAE reporting tool to comprehensively assess surgical outcomes</td>
<td>53</td>
</tr>
<tr>
<td>Sung Hyon Han</td>
<td>Biomechanics of Cantilevered Implant-supported Prosthesis</td>
<td>54</td>
</tr>
<tr>
<td>Maya Harary</td>
<td>Application of functional neurosurgery techniques to treat children with fragile X syndrome</td>
<td>55</td>
</tr>
<tr>
<td>Gillian Horwitz</td>
<td>BMI as predictor of adverse outcomes with intravenous sedation during surgical abortion</td>
<td>56</td>
</tr>
<tr>
<td>Anne Huang</td>
<td>A Single Center’s Experience with Donation of Facial Allografts for Transplantation</td>
<td>57</td>
</tr>
<tr>
<td>Jaeho Hwang</td>
<td>Somatic Genetic Biomarkers of Bevacizumab Response in Glioblastoma Multiforme</td>
<td>58</td>
</tr>
<tr>
<td>Masis Isikbay</td>
<td>The Implications of TMPRSS2:ERG Fusion Status In Prostate Cancer</td>
<td>59</td>
</tr>
<tr>
<td>Helen Jack</td>
<td>The role of recovery coaches in community-based treatment of substance use disorder</td>
<td>60</td>
</tr>
<tr>
<td>Otana Jakpor</td>
<td>Association between Birth Weight, Fine Particulate Matter (PM2.5) &amp; Meteorological Factors</td>
<td>61</td>
</tr>
<tr>
<td>Iny Jhun</td>
<td>School Air Cleaner Intervention to Improve Indoor Air Quality for Children with Asthma</td>
<td>62</td>
</tr>
<tr>
<td>Yisi Ji</td>
<td>Impact of a Dental Team on Documentation of Oral Health Findings among Patients in a Student-Faculty Collaborative Clinic</td>
<td>63</td>
</tr>
<tr>
<td>Manjinder Kandola</td>
<td>Identifying Factors Related to the Adoption and Sustained Use of Consumer Activity Tracking Devices and Applications</td>
<td>64</td>
</tr>
<tr>
<td>Aditya V. Karhade</td>
<td>Predictors of post-operative infections in neurological surgery: analysis of 94,000 patients</td>
<td>65</td>
</tr>
<tr>
<td>Andrew Kim</td>
<td>Characterization of Hydrocephalus and its Neurosurgical Interventions in Arusha</td>
<td>66</td>
</tr>
</tbody>
</table>
Tanzania

John Klecker  Medication Related Osteonecrosis of the Jaw: Effect of Acidic Milieu on Osteoclast Function  67

Margaret Krasne  Understanding Barriers to Uptake of WHO Safe Childbirth Checklist in India: A Mixed Methods Analysis of Opportunity-Able-Motivation (OAM)  68

Joshua Ladner  Magnetic Resonance Spectroscopy of Mild Traumatic Brain Injury and Posttraumatic Stress in the Military  69

R. Frederick Lambert  Factors that motivate otherwise healthy HIV+ young adults to access HIV testing and treatment in Gugulethu, South Africa: A qualitative study  70

Dalia Larios  Students as health coaches and change agents at Brookside Community Health Center: a tool to improve health outcomes in diabetic patients  71

Alexandra Larsen  Urinary biomarkers correlate with preoperative disease status, presence of transdural collaterals and predict 1-year angiographic outcomes in pediatric moyamoya patients  72

Claire Learmonth  Perceptions of Rwanda’s Medical Postgraduate Programs Qualitative analysis of trainee and faculty perceptions of a medical education intervention  73

Charlotte Lee  Proteomic Profiling to Elucidate Intratumoral Heterogeneity and Cancer Evolution in Lung Cancer  74

Daniel Lee  Identifying a Role for the Posterior Temporal Lobe in Grammatical Processing  75

Samuel Lee  Impact of Restorative Treatment on Oral Health-Related Quality of Life in Patients in Ireland with Hypodontia – A Two-year Follow-up Observation Study  76

Stephanie Lee  Evaluation of the Dental Vibe Injection Comfort System  77

Suk Joon Lee  Simulation of Paravalvular Leak (PVL) after Transcatheter Aortic Valve Replacement (TAVR)  78

Howard Li  Characterizing the Response of a CDK Inhibitor Family to Anti-proliferative Stress  79

Kevin Liu  Characterizing Molecular Pathways that Regulate Tumor Immune Resistance in Esophageal Adenocarcinoma  80

Damir Ljuboja  The Expansion of Digital Clinical  81
Tracy Lu  Barriers to Health for the Homebound Ill: Patients’ Perspectives  82
Claudio Macias  Circulating Growth Differentiation Factor 11/8 Levels Decline with Age  83
Trevino  Brain Activity Mapping in Tsc1 Mutant Mice to Identify Macrocircuit Abnormalities  84
Rebecca MacRae  Combatting Decision Fatigue in the Emergency Department  85
Keenan Mahan  Experiences, beliefs, and attitudes about cervical cancer screening among women in Pietermaritzburg, KwaZulu-Natal, in South Africa: A qualitative study.  86
Camille Mathey-Andrews  Understanding the role of tumor-derived extracellular vesicles in breast cancer metastasis  87
Michael McClurkin  Correlation of 3D Neuroretinal Rim Thickness and Visual Fields in Glaucoma: A Broken Stick Model  88
Kalie McCulloch  Efficacy of Icon Application on White Spots of Various Etiologies - A Pilot Study  89
Stephanie McNamara  A Refillable Anti-Thrombogenic Surface Treatment for Vascular Devices  90
Diana Miao  Genomic predictors of response to CTLA4 blockade in metastatic melanoma  91
Kathleen Miller  The Impact of an Option B+ Prevention of Mother to Child Transmission Program on HIV+ Mothers in Mbarara, Uganda  92
Jason Mitchell  Genetic Expression Profiling of Ovarian Cancer Cells treated with Mullerian Inhibiting Substance  93
Kellie L. Moore  Assessing oral health knowledge and behaviors of residents of the province of Loreto, Peru  94
Mary Morales  Food Insecurity and Cardiovascular Health in Pregnant Women: Results from the Food for Families Program  95
Ramya Mosarla  Predictors of Disease Progression during Surveillance of Patients with Asymptomatic Carotid Artery Stenosis  96
Jessica Mueller  Global Benchmarking of Risk-Adjusted Surgical Outcomes: A Pilot  97
Rumbidzai Mushavi  Water insecurity and emotional distress: population-based, mixed methods study in rural Uganda  98
Anirudh Nandan  The Impact of Intraoperative Adverse Events on Hospital Readmission  99
Kelsey Natsuhara  Determinants of Unrepaired Third and Fourth Degree Perineal Lacerations  100
<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contributing to Obstetric Fistula Burden: An Assessment of Senior Midwife Trainers in Western Kenya</td>
<td>101</td>
</tr>
<tr>
<td>Michael Nguyen</td>
<td></td>
</tr>
<tr>
<td>The impact of body habitus on the outcomes after aneurysmal subarachnoid hemorrhage: A nationwide analysis</td>
<td></td>
</tr>
<tr>
<td>Laura Nicholson</td>
<td>102</td>
</tr>
<tr>
<td>An evaluation of attitudes among members of the Navajo Nation community towards the availability and affordability of healthy and traditional Navajo foods in local stores</td>
<td></td>
</tr>
<tr>
<td>Deyang Nyandak</td>
<td>103</td>
</tr>
<tr>
<td>Adequacy of Prenatal Care and Sex Ratios in Humans</td>
<td></td>
</tr>
<tr>
<td>Benjamin L. Palla</td>
<td>104</td>
</tr>
<tr>
<td>Systematic Review of Oral Ulceration with Bone Sequestration</td>
<td></td>
</tr>
<tr>
<td>Marissa C. Palmor</td>
<td>105</td>
</tr>
<tr>
<td>Assessing the implementation of a program to improve serious illness conversations in a high-risk care management program in the primary care setting</td>
<td></td>
</tr>
<tr>
<td>Raymond Parrish</td>
<td>106</td>
</tr>
<tr>
<td>Patient Satisfaction and its Relation to Perceived Visit Duration with a Hand Surgeon</td>
<td></td>
</tr>
<tr>
<td>Achyut Patil</td>
<td>107</td>
</tr>
<tr>
<td>Evaluation of a diabetes performance improvement initiative in primary care</td>
<td></td>
</tr>
<tr>
<td>Elizabeth Perry</td>
<td>108</td>
</tr>
<tr>
<td>Transcriptional Co-activator PGC1alpha Protects Cartilage from Osteoarthritis</td>
<td></td>
</tr>
<tr>
<td>Yasameen Pirooz</td>
<td>109</td>
</tr>
<tr>
<td>Effect of Social Media on Dissemination of Preventive Oral Health Measures Through Accessible Online Learning Modules in Rwanda</td>
<td></td>
</tr>
<tr>
<td>Chloé Powell</td>
<td>110</td>
</tr>
<tr>
<td>Maternal experiences of racial discrimination and offspring sleep in the first 2 years of life</td>
<td></td>
</tr>
<tr>
<td>Naveed Rabbani</td>
<td>111</td>
</tr>
<tr>
<td>Transcriptome Analysis of Wnt Signaling Pathway in Pediatric Hepatocellular Carcinoma</td>
<td></td>
</tr>
<tr>
<td>Faith Robertson</td>
<td>112</td>
</tr>
<tr>
<td>The Impact of Early Intervention on the Outcomes after Decompressive Cranietomy for Stroke: A Nationwide Analysis</td>
<td></td>
</tr>
<tr>
<td>Victoria Robson</td>
<td>113</td>
</tr>
<tr>
<td>Copy Number Variation Contributes to the Phenotypic Variability of Syndromic Duane Retraction Syndrome</td>
<td></td>
</tr>
<tr>
<td>George Romar</td>
<td>114</td>
</tr>
<tr>
<td>Neutrophil-mediated Dermatoses in Neutropenic Patients</td>
<td></td>
</tr>
<tr>
<td>Sara Rosenberg</td>
<td>115</td>
</tr>
<tr>
<td>An Exploration of the Oral Health Knowledge, Attitudes and Behaviours about School-based Oral Health Education of 11-14 Year Old School Children</td>
<td></td>
</tr>
<tr>
<td>Robert Rudy</td>
<td>116</td>
</tr>
<tr>
<td>Risk of Rupture of Intracranial Aneurysms:</td>
<td></td>
</tr>
</tbody>
</table>
A Systematic Review and Meta-analysis by Aneurysm Location

Priyanka Saha
Development of a Web-Based Resource Directory for Improving Pediatric to Adult Healthcare Transitions in the Medical Home

Rohit Sahdev
A Retrospective Single-Center Study on Patient Outcomes Following Total Temporomandibular Joint Replacement Surgery

Alfonso Salcines
Post-Operative Stability of Distraction Osteogenesis of the Mandible

Christine Santiago
A Volumetric MRI Study of the Basal Ganglia in Geriatric Patients with Bipolar Disorder

Lauren Schleimer
“Ou Menm Ak Kansè”: Developing an Educational Booklet for Patients with Cancer in Haiti

Joseph Sedlak
In vitro validation of immune resistant genetic changes in cancer

Y. Raymond Shao
Developing preoperative assessments of brain function to improve anesthetic care in elderly patients

Jonathan Shapiro
Regional Differences in Caries Prevalence in Icelandic Six Year Olds

Krishan Sharma
Evaluation of Acute Respiratory Distress Syndrome (ARDS) in Patients Enrolled in the Protocolized Care for Early Septic Shock (ProCESS) Trial

Ashley Shaw
A Qualitative Evaluation of Student and Patient Perceptions of a Palliative and End-of-Life Care Curriculum taught in the Nursing Home

Andre Shomorony
Extracorporeal Immune Modulating Therapy for Sepsis

Colleen Sinnott
Quality of life assessment following cardiac surgery in a resource-limited setting: Rwanda

Robert Smalley
Identification of a Novel Population of Neurons Involved in Pain Perception

William Smith
Getting to Zero: Reducing HIV Incidence through Screening, Treatment, and Prevention

Jiunn Song
Development of a new zebrafish model for studying cell-autonomous connexin mutants linked to atrial fibrillation

Vishwajith Sridharan
Effects of definitive chemoradiation on circulating angiogenic cytokines in head and neck cancer patients

Kate Stoeckle
Interviews of Doctors and Nurses Pre- and
Fangdi Sun
The Need for Preoperative Baseline Arm Measurement to Accurately Quantify Breast Cancer-related Lymphedema

Monica Tain
Learning Resource Used Versus Usefulness in the Basic Sciences Curriculum

Zujaja Tauqeer
Medicine as a lens into the political history of a postcolonial state

Jacob T. Taylor
Evaluating the Health Literacy Environment of Hospitals and Health Centers in Barcelona to Improve the Quality of Care

Megan Townsend
Creation of a Community Advisory Board for Community-Based Cancer Research in Navajo Nation

Hanh Truong Tran
Understanding the Public’s Perspective on the Integration of Medicine and Dentistry

Emily Unger
Determining Barriers to Maternal and Neonatal Care to Prevent Neonatal Mortality in Eastern Rwanda

Eugene Vaios
Characterization of bone marrow response as a potential biomarker of clinical outcome in patients with glioblastoma

Yannis Kalogirou Valtis
Evidence-based clinical resources in sub-Saharan Africa: Understanding and promoting their usage

Danny Vazquez
Posttraumatic Stress Disorder in Young Breast Cancer Survivors

Carolynn Vuong
A Retrospective Cohort Study of Medi-Cal’s Reinstatement and Its Effects on Dental Service Utilization

Cameron Waites
Defining the Mechanisms of Axon Growth after Limb Amputation

Amy Wang
Developing a novel cortical-to-spinal neural prosthesis for restoring volitional movement in awake-behaving animals

David Wang
Assessment of Teamwork Attitudes among Interdisciplinary Healthcare Team Members in the Program of All-Inclusive Care for the Elderly (PACE) Model

Kathy K. Wang
Characteristics of Hospitals Penalized the Most by Federal Pay-for-Performance Programs

Thomas Wang
Defining the Role of IL-33 Producers in Skeletal Muscle Repair and Disease

Debra Whorms
Quality Assessment of Diabetes Care Provided at PIH-Supported Non-Communicable Diseases Clinics in Rwanda using EMR-Retrieved Data
Chloe Wong  
Accuracy of and Compliance with Established Risk Stratification Guidelines for Febrile Neutropenia in the Emergency Department  

Danny Wong  
Role of MicroRNA-181b in Regulating Hydrogen Peroxide Signaling in Endothelial Cells  

Michael P. Wu  
Expression of FOXJ1 and the Ciliogenesis Gene Program in Glioblastoma  

Winona Wu  
The Role of Intermittent Hypoxia in the Pathogenesis of Non-Alcoholic Fatty Liver Disease  

Ryan Xiao  
Corticosteroid Injections for Adhesive Capsulitis: A Review  

Liwen Xu  
Application of Whole Exome Sequencing to the Genetic Diagnosis of Limb-Girdle Muscle Weakness  

Zihao Yan  
Yield of CT Pulmonary Angiography in the Emergency Department when Providers Override Evidence-Based Clinical Decision Support  

Brian Yang  
Market Analysis: Orthopedic Medical Device FDA 510(k) vs. PMA Approval Feasibility  

Leigh Yarborough  
A Storybook Approach to Oral Health Education in Primary School Children  

Hannah Yoo  
Developing Effective Communication Strategy for Global Oral Health Interest Group  

Grace Young  
An investigation of skin biopsy outcomes for evaluation of acute-onset erythematous nodules in immunocompromised children  

Amy Yu  
Pain Management among Dominican Patients with Advanced Arthritis: A Qualitative Study  

Golmah Zarinkhou  
Dental Curricula, CODA, and Patients with Special Needs: Where Are We Now?  

Biqui Zhang  
Predicting Isocitrate Dehydrogenase Mutation Status and Survival Outcome in High-Grade Gliomas with Multimodality Imaging Markers  

Connie Zhao  
Characterizing a novel small molecule inhibitor of HIV-1 Env-mediated entry, PF-68742  

**Current Year 3 Students**  

Melanie F. Molina  
Emergency Department-Based Needs Assessment from a Safety Net Hospital in South Los Angeles  

Sumi Sinha  
Title: Systemic Delivery of Opsins to...
Cochlear Nucleus Neurons Using Adeno-Associated Virus

Elisa C. Walsh
Characterization of the Propofol-Induced Frontal Encephalogram in Autism Spectrum Disorder (ASD)

Current Year 4 Students

Vishesh Agrawal
Evaluation of CT Imaging Features of Non-Small Cell Lung Cancer During Chemoradiation

Cary Crall
Quality of Life in Children with Cutaneous Stigmata of Tuberous Sclerosis Complex

Samuel Dickman
Fifty Years of Health Spending by Low, Middle, and High-Income Americans and Implications in the Era of Increased Cost Sharing

Andrey V. Dolinko
Patients with systemic cancer have lower ovarian reserve and require higher gonadotropin doses for fertility preservation

Vikas Gampa
The Cultural Elements Underlining the Community Health Representative – Client Relationship in Navajo Nation

Jordan Garcia
Optical Coherence Tomography for Noninvasive Imaging of the True Vocal Fold

David Kuppermann
Diagnostic success and prediction of tumor subtype of renal mass biopsy improves with experience: longitudinal results in a single series cohort of 1233 tumors

Charles Liu
Creation and Validation of a Brief Surgical Procedure Code List for Outcomes Research in Resource-Limited Settings

Diana López
“Non-Functional” Adrenal Adenomas and Incident Cardiometabolic Outcomes

Clara Men
Sequence-specific suppression of alleles causing dominantly inherited retinal degenerations using the RNA-guided nuclease Cas9

Abirami Natarjan
Provider experiences with uterine balloon tamponade for uncontrolled postpartum hemorrhage in health facilities in Kenya

Anna Alaska Pendleton
Emergency hysterectomy for uncontrolled postpartum hemorrhage may be averted through uterine balloon tamponade in Kenya and Senegal

Nathaniel Roysden
Prediction of Healthcare Utilization Following Behavioral Health Encounter Using Natural Language Processing and Machine Learning
<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jinesh Shah</td>
<td>National Trends in Incidence of Acoustic Neuromas Based on the Nationwide Inpatient Sample Database.</td>
<td>184</td>
</tr>
<tr>
<td>Christina H. Shin</td>
<td>Effect of Obstructive Sleep Apnea Risk on Postoperative Respiratory Complications</td>
<td>185</td>
</tr>
<tr>
<td>Diana Wohler</td>
<td>Committed to Leadership: A Landscape Analysis of Leadership Training in the Medical School Curriculum</td>
<td>186</td>
</tr>
<tr>
<td>Min Wu</td>
<td>Trends in Direct-to-Consumer Advertising of Prescription Contraceptives</td>
<td>187</td>
</tr>
</tbody>
</table>
Year 2
Abstracts
Clinical and Genetic Investigation of Patients with Recurrent Arterial Dissections

Mohammad H. Abbasi
Harvard Medical School, Francis Weld Peabody Society, Class of 2018

Mark E. Lindsay, MD, PhD
Cardiovascular Research Center
Massachusetts General Hospital
Harvard Medical School

Arterial dissections occur in various anatomic distributions, including the aorta and the cervical, mesenteric, or coronary arteries. Aortic dissection (AoD), and in particular dissection of the ascending aorta, is the most common type of arterial dissection. A rare population of individuals experiencing AoD may experience a second AoD (recurrent AoD) or may experience a dissection elsewhere in the vasculature. We hypothesized that these recurrent arterial dissection (RAD) events may be underappreciated in AoD populations.

Using the Research Patient Data Registry (RPDR) we have identified 75 patients with RAD. Of 75 patients, 50 (66.7 %) had recurrent AoD, 23 (30.7 %) had AoD and cervical artery dissection, 4 (5.3 %) had AoD and mesenteric artery dissection, and 2 (2.7 %) had AoD and coronary artery dissection. These patients represented our experimental group and were compared to 162 patients with a single episode of AoD (SAD). Multiple differences were noted between RAD and SAD patients. RAD patients were significantly younger (46.0 ± 16.1 years vs. 65.9 ± 14.6 years, \(p \lt 0.001\)) and had less hypercholesterolemia (32.0 % vs. 58.6 %, \(p \lt 0.001\)), less coronary atherosclerosis (38.7 % vs. 63.0 %, \(p \lt 0.001\)), fewer myocardial infarctions (25.3 % vs. 45.7 %, \(p \lt 0.001\)) and more mitral valve disease (54.7 % vs. 42.0 %, \(p=0.03\)). RAD patients were enriched for the condition Marfan syndrome (MFS), which accounted for one-third of patients (32.0 % vs. 5.6 %, \(p \lt 0.001\)).

MFS was present in a sizable fraction of RAD patients, and therefore we asked whether observed differences were attributable to its presence in our experimental group. Interestingly, reanalysis of the data excluding MFS patients documented persistent trends in study variables. Most strikingly, non-MFS RAD patients were still younger than their non-MFS SAD counterparts at the time of their first AoD by over a decade (54.8 ± 13.5 years vs. 67.5 ± 13.4 years, \(p \lt 0.001\)). Non-MFS RAD still show less hypercholesterolemia (39.2 % vs. 61.4 %, \(p=0.001\)) and coronary atherosclerosis (43.1 % vs. 66.0 %, \(p=0.001\)) than non-MFS SAD patients. Importantly, the association between mitral valve disorders and RAD was lost in this reanalysis, as would be expected for a non-aortic phenotype closely associated with MFS.

In conclusion, RAD appears to be a clinical marker for MFS. Additionally, and perhaps more importantly, RAD appears to be a harbinger of underlying, genetically-triggered aortic disease. These data have important implications for clinical care and genetic screening of patients with AoD.
A Qualitative Exploration of Community Health Work in Lebanon

Nora Abo-Sido
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Lara Jirmanus, MD
Global Women's Health Fellow
Brigham and Women's Hospital

Around the world, community health workers (CHWs) provide a wide range of services including but not limited to health education, diagnosis and treatment of common illnesses, maternal and child health, and chronic disease management. CHWs are increasingly used to address health worker shortages. Although Lebanon has 3.2 physicians per 1000 people, underprivileged populations often suffer from lack of healthcare access due to cost. The influx of over one million Syrian refugees has placed an additional burden on an already strained health system. Although literature on community health work in the Middle East is lacking, NGOs are increasingly using lay people to deliver health care to underserved populations in Lebanon. This study sought to describe the scope of work of CHWs in Lebanon, as well as motivations and challenges faced by CHWs.

The qualitative study used stratified purposeful selection to select 11 CHWs (10 female and one male) from 5 NGOs in a variety of geographical locations serving different populations, including Lebanese, Syrians and Palestinians. Semi-structured, in-depth interviews were conducted in Arabic by a single interviewer. Interviews explored the scope of CHW practice in differing settings, CHW training and supervision, as well as CHW motivations and barriers. Through a comparison of CHW experiences across the country we sought to identify best practices and appropriate CHW skillsets for the Lebanese context, as well as describing challenges faced by CHWs and strategies for overcoming them. Interviews were translated and transcribed by the interviewer and a research assistant fluent in Levantine Arabic and coded thematically by two independent coders.

Many of the community health workers primarily focused on health education, while few performed home visits. None of the community health workers delivered direct care, such as prescribing medicines or delivering vaccines. Community health workers described gender equality and women’s empowerment to be important motivators for community health work.

Although the number of study participants is small (11), this exploratory study identifies examples of a form of health delivery that is relatively limited in Lebanon. The sample size was further limited by the sociopolitical climate at the time, as it was not possible to travel to certain areas of Lebanon.

By describing existing community health work in Lebanon, as well as CHW motivations and challenges, this study lays the foundation for the development of further CHW initiatives in Lebanon and the region.
Listening for a Patient’s Story: Identifying Themes of the Patient-Doctor Relationship through Narrative Patient Interviews

Michael A.D. Alcalá
Harvard Medical School, Cannon Society, Class of 2018

Susanne Klingenstein, PhD
Harvard-MIT Division of Health Sciences and Technology

A patient’s experience with a physician is often shaped by the few minutes of interaction they share during their brief encounter. But seeing eye-to-eye with a patient, that is—understanding the concerns and story of a patient—comes not just by listening to a patient’s story but by listening for the story. The ability to tell a patient’s story and capture its meaning can be used to help establish empathy throughout the patient-doctor relationship. Analogous to learning about medicine by looking at art, reflective writing enables the medical student to learn on their own about the patient-doctor relationship by examining their patients’ stories instead of simply relying on a supervising physician to teach them. We hypothesized that careful observation and listening throughout a patient interview allows a medical student to perceive differently; and that detailed writing about the encounter builds linguistic sensitivity that allows a medical student to communicate the lessons of one interview to other interviews, thereby enhancing the learning process.

There is a lot to be learned in each patient encounter, and much of this does not get written into the patient’s chart. The study was intended to capture this lost information by writing narrative reflections—a collection of short stories about my patient encounters from my first year of medical school—to generalize some lessons learned about the patient-doctor relationship. Prose and dialogue were used as the main tools in weaving a short story together, similar to how dialogue is used by a clinician to uncover the patient’s history and story.

Twelve narratives were written, while three of these stories were chosen for further and ongoing editing to fit into 1-3 pages of text per story to prepare for manuscript submission, highlight certain themes of the patient-doctor relationship. While each patient presented with a constellation of symptoms that were previously described in the literature, their stories of how they experienced their condition were unique in their own way. Writing the patient’s story enabled me to better learn about the patient as a person, and focus my attention on how they experienced their condition.
Survival Roles for RagA and RagB in Acute Myeloid and T-Cell Acute Lymphoblastic Leukemias

Amir H. Ameri
Harvard Medical School, Francis Weld Peabody Society, Class of 2018
TargetCancer Medical Student Research Fellowship

David T. Scadden, MD
Center for Regenerative Medicine, Department of Hematology/Oncology
Massachusetts General Hospital

Acute leukemias are among the most common cancers and often relapse after chemotherapy and bone marrow transplantation. Mechanistic target of rapamycin complex 1 (mTORC1), a multiprotein regulator of cell metabolism, is implicated as a driver in acute myeloid leukemia (AML) and T-cell acute lymphoblastic leukemia (T-ALL). However, current pharmacological inhibition of mTORC1 is either incomplete, as in the case of rapamycin, or non-specific, as new generation catalytic site inhibitors block mTORC2 as well. One strategy for specific and complete inhibition of mTORC1 signaling is to block lysosomal localization of mTORC1 and, effectively, its activation in response to nutrients, including amino acids. This strategy will inhibit mTORC1 protumorigenic functions, while reducing toxicity to normal cells by preserving the amino acid-independent function of mTORC2. RagA (Ras-related GTP binding A) and RagB (Ras-related GTP binding B) are GTPases required for the amino acid-mediated activation of mTORC1, specifically recruiting mTORC1 to the lysosome in response to amino acids, where mTORC1 is activated by growth signals.

We hypothesized that inhibiting lysosomal localization of mTORC1 would selectively inhibit growth of T-ALL and AML cells. To test this hypothesis, we reduced expression of RagA and RagB, essential components of the amino acid-sensing arm of the mTORC1 pathway. In the AML cell line, U937, one of two lentiviral-delivered, RagA-targeted shRNA hairpins reduced viability (CellTiter 96 Aqueous One assay). Both hairpins reduced RagA protein levels and expression of pS6, a surrogate marker for mTORC1 signaling. RagB-targeted shRNA inhibited RagB expression and cell viability (2/2 hairpins) in U937 cells, although pS6 levels were not consistently reduced. In the T-ALL cell line, JURKAT, depletion of RagA inhibited cell viability (2/2 hairpins) and slightly reduced expression of RagA. Due to the low shRNA-mediated knockdown of RagA observed in some cell lines, oligonucleotides were designed and cloned into lentiviral vectors to produce guide RNA and Cas9 protein in transduced cells for CRISPR-Cas9 genome editing/deletion. More replicates of the cell viability assay are required to determine the role of nutrient sensing by mTORC1 in leukemia. However, these preliminary data suggest a pro-viability role for the Rag GTPases and mTORC1 regulation specifically by nutrients in AML or T-ALL.
Establishing a pipeline to discover the T cell repertoire after neoantigen vaccine using paired TCRαβ chain single cell sequencing

Annabelle J. Anandappa
Harvard Medical School, Irving M. London Society, Class of 2018

Catherine J. Wu, MD.
Department of Medical Oncology
Dana Farber Cancer Institute

The clinical success of checkpoint blockade demonstrated that endogenous T cells are capable of recognizing tumor antigens through their T cell receptors (TCRs) and eliminating tumor cells. It also renewed enthusiasm for cancer vaccines, which in combination with checkpoint blockade may amplify anti-tumor T cell responses. Neoantigens are T cell targets, derived from DNA alterations that result in the formation of novel protein sequences. These epitopes are appealing targets for cancer vaccines because they are exquisitely tumor-specific. Next generation sequencing together with algorithms that predict immunogenicity have enabled the identification of patient-specific neoantigens.

This strategy was applied to develop NeoVax, a personalized neoantigen vaccine currently undergoing a Phase I clinical trial that was designed to prevent recurrence in patients with surgically resected melanoma. Following vaccine administration, traditional immunologic assays can be employed to monitor neoantigen-reactive T cells and assess changes in the patient’s immune response. However, high throughput methods to identify the TCR sequence of anti-tumor T cells and determine their antigen targets are lacking.

To address this challenge, we are building a pipeline that employs single cell sequencing to study TCRs. Analyzing at single cell level enables paired sequencing of the TCRα and TCRβ chains, which together encode the specificity of the TCR. Sequence information from the complementarity-determining region 3 (CDR3) is sufficient to reconstruct the complete TCR. We designed a library of TCR expression vectors, which includes the full repertoire of Variable α (Vα) and Variable β (Vβ) s. Any TCR sequence of interest can be constructed by combining pre-made V constructs with two custom-synthesized oligonucleotides that encode the CDR3 region of the α- and β-chains using Golden Gate Assembly.

To perform antigen determination, a reporter cell line was generated from a TCR-deficient Jurkat cell line. It was modified to express a reporter construct that encodes the fluorescent protein mCherry under the control of six NFAT response elements. When TCRs are expressed in the reporter cell line and stimulated with their cognate antigen, downstream signaling pathways lead to mCherry expression, enabling identification of their target antigens. The same expression system can be used to express TCRs in PBMCs to assess cytokine production and cytotoxicity. This innovation will allow us to more precisely validate and optimize the peptide prediction algorithms used in designing the vaccines and improve our understanding of the critical tumor antigens targeted by the immune system to elicit the most potent anti-tumor response.
Analysis of variation over time in bundled payment costs

Jordan D. Anderson
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Sree Chaguturu, MD
Population Health Management
Partners Healthcare

The fee-for-service payment model has been noted for its inability to reduce costs or incentivize coordination between various healthcare providers involved in a patient’s episode of care. One alternative payment methodology designed to encourage efficiency and care coordination groups a set of services for a defined episode of care into a single fixed payment. This “bundled payment” model has been supported by Medicare and many private payers, however there is limited research looking at the degree to which bundled payment costs vary over time.

This lack of research has led to worries within the provider community that bundled payments will place physicians at financial risk for significant random variation between episodes that cannot be managed by the care team and are not accounted for within the risk adjustment model. Research assessing variation in bundled payment reimbursements has used simulation-based modeling; however analyses of real Medicare claims data is more limited.

We hypothesized that there would not be significant variation in bundle payment costs year-over-year. To test this hypothesis we used Medicare claims data collected from the Partners Healthcare, Pioneer ACO Medicare population. From this dataset we organized patient medical claims from 2012 to 2014 into 90-day bundles for joint replacement of the lower limb (MS-DRG 469 and MS-DRG 470) using the Medicare grouper definition and then assessed the variation in bundled payment costs year-over-year. We analyzed MS-DRG 470 and MS-DRG 469 independently to account for the complications and co-morbidities that are indicated in the MS-DRG 469 classification.

Based on preliminary results for joint replacement of the lower limb without complications or co-morbidities (MS-DRG 470), we identified significant variation in mean bundle cost from 2012 to 2013 (Mean: 31,576; 29,881 respectively, p<.05), as well as from 2013 to 2014 (Mean: 29,881; 31,664 respectively, p<.05). In patients with complications and co-morbidities (MS-DRG 469), we did not identify significant variation in mean bundle costs year-over-year.

These data indicate that variation in mean bundle costs exists year-over-year among patients without complications or co-morbidities. Identifying significant variation in patients without complications and co-morbidities could indicate a poor risk-adjustment model that leaves too much clinical and cost variation in the MS-DRG 470 classification. As CMS and other payers begin to implement bundled payments for episodes of care, both physicians and policy-makers should be aware of the variation that can exist in these payments across time.
More than 100 years after the Flexner report, medical education continues to be improved. Medical schools across the country have recently undergone or are currently undergoing curricular reforms. Moreover, rising health care costs and the health care reforms that they helped to precipitate have brought value questions into focus. In light of these tectonic forces and the importance of training physicians capable of practicing in the 21st century, I sought to explore the education mission of medical schools.

This project had three primary goals: (1) to investigate through a journalistic piece the role of value based medicine in undergraduate medical education, (2) to explore high value care programs at medical institutions across the country, and (3) to examine the education mission within the larger medical school apparatus.

In order to investigate the role of value based medicine in undergraduate medical education, I interviewed approximately 20 medical education stakeholders from a variety of institutions were interviewed. In addition, literature on the topic of value-based medicine was analyzed. These interviews while informative did not provide a compelling argument around which to structure a journalistic piece. I may revisit this topic in the future as additional experiences in value-based medicine are acquired.

Furthermore, a manuscript exploring high-value care education programs was composed with Dr. Brandon Combs at the University of Colorado. Topics discussed in the manuscript included programs at the Medical College of Wisconsin and at UCSF to train medical students to be high-value care officers. This manuscript was accepted for publication in the November issue of the AMA Journal of Ethics.

Finally, with the help and supervision of Dr. Richard Schwartzstein, I worked towards writing a perspective piece that examines the role of the education mission within the larger medical school apparatus. Work on this component of the project is ongoing.
A Systematic Review of National Policies on Tuberculosis Contact Investigations

Soraya Azzawi
Harvard Medical School, Francis Weld Peabody Society, Class of 2018

Dr. Mercedes C. Becerra, Sc. D and Dr. Courtney M. Yuen, Ph.D
Department of Global Health and Social Medicine
Harvard Medical School

Although the prevalence of tuberculosis (TB) has been slowly declining, TB claimed an estimated 1.5 million lives in 2013. Furthermore, only two thirds of the world’s 9 million new TB cases were diagnosed and reported to TB programs in 2013. Contact investigation— in which close contacts of TB patients are promptly evaluated and treated for TB disease and infection— is an effective strategy for finding, treating, and preventing TB. The World Health Organization (WHO) estimates that contact investigation could detect at least 300,000 early TB cases annually. In 2012, WHO published recommendations for performing contact investigations for TB patients in low- and middle-income countries.

The success of this recommendation is ultimately contingent upon the strength and content of each country’s TB policy. As a step towards the routine implementation of contact investigations, it is imperative to understand the quality of guidance available at national levels. To address this need, we conducted a systematic review of national policies on TB contact investigation, assessing each guideline’s strength and content. To date, no systematic review of national policies on TB contact investigation has been published.

Utilizing standardized search terms, we conducted a systematic Internet search for 216 country and territory guidelines. If we were unable to find a guideline, we contacted the National Tuberculosis Program. We included national-level guidelines for general TB control or contact investigations that were published in English, Spanish or French. We extracted data using a standardized collection form with double-extraction and reconciliation by consensus.

Of 216 countries and territories searched, we obtained 84 (39%) guidelines, 69 (82%) of which met our language inclusion criteria. All contain recommendations on contact investigations. For the 22 high-burden TB countries, which contain 80% of all TB cases, 12 (55%) guidelines were found and included. While all recommend contact investigation, this is an enforceable activity in only one (8%) of these countries. Moreover, three (25%) high-burden country guidelines place the responsibility for its completion on the patient rather than the health system, and four (33%) do not specify how evaluation of contacts should be ensured. Only six (50%) recommend evaluating contacts for TB infection, although 11 (92%) contain recommendations for treating infection.

Guideline collection and data extraction are ongoing. Analysis will be stratified by geographic region, TB incidence and income level. This study will create a foundation for future research to identify gaps between policies and practice.
Trends in Orthognathic Surgery

Lauren Azzopardi
Harvard School of Dental Medicine, Oliver Wendell Holmes Society, Class of 2018

Katherine Klein DMD, MS
American Board of Orthodontics
Massachusetts General Dental Group

Orthognathic surgery corrects abnormalities of the maxilla, mandible, or both and may be used to resolve common disorders, such as sleep apnea and Temporomandibular Joint Disorder (TMJD). Previous studies, literature and clinical experience have shown that orthognathic surgery results in the improvement of multiple functional parameters.

Patients with an improper bite or incorrectly positioned jaws can benefit from orthognathic surgery, often referred to as corrective jaw surgery. Jaw injury, birth defects, and variation in upper and lower jaw growth rates can affect alignment of the jaw. The resulting problems affect chewing function, nutrition, speech, long-term oral health and general health, and physical appearance. Orthodontics alone can correct bite problems when only the teeth are involved, however orthognathic surgery may be required for repositioning of the jaw.

Occlusion can be classified as Class I, Class II, or Class III. Class II and III are potential candidates for having orthognathic surgery. Candidates for orthognathic surgery are often analyzed for comorbidities such as obstructive sleep apnea (OSA) and mental health concerns. There are few published data that document the characteristics and possible rationale of patients seeking orthognathic surgical treatment.

In the creation of an ongoing database for surgical orthodontic patients at Massachusetts General Hospital, the number of surgical patients with Class I, class II, or class III malocclusion, OSA, and mental health documentation was analyzed. The information obtained gives insight into the population of patient seeking surgical orthodontic treatment, and gives information about the type of surgery typical orthognathic treatment requires, as well as the reasons and thus desired outcome of the patient.

We hypothesized that patients with class III malocclusion would be more likely to seek orthognathic surgery for more severe disturbances in function and esthetics. We also hypothesized that the percentage of patients seeking orthognathic surgery with OSA would be significantly greater than the percentage of OSA in the general population, implying that OSA is a large patient motivator for seeking obstructive sleep apnea. It was also hypothesized that there would be a significant percentage of patients with mental health documentation, giving further insight into the surgical patient population and implications for positive psychosocial outcomes after surgery.

Results are pending.
Implementing E-Visits in Partners Primary Care Practices

Francesca G. Barrett
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

Jeffrey A. Linder, MD, MPH, FACP
Division of General Internal Medicine & Primary Care, Department of Medicine
Brigham and Women’s Hospital

Patients want easily accessible care when problems or medical questions arise. Primary care practices have failed to keep pace with this desire, fueling new models of care – retail clinics, urgent care centers, and internet-based medical care companies – that disrupt continuity of care. Primary care practices could potentially better maintain continuity and improve access and capacity by providing more efficient, asynchronous non-visit based communication and advice.

E-Visits are a novel method of asynchronous healthcare delivery. E-Visits are patient-initiated structured questionnaires regarding an acute, non-emergent health care problem. Patients complete E-Visits about select problems on an online patient portal and submit them to their primary care practice. During a pilot implementation, we assessed the volume of E-Visits and patient satisfaction with E-Visits.

In July 2015, the Brigham and Women’s Primary Care Practice Based Research Network implemented E-Visits at 2 practices for 8 acute medical problems: acute cough, back pain, heartburn, sinusitis, urinary tract infection, red eye, diarrhea, and vaginal complaints. At the start of the implementation, we conducted phone surveys with patients who completed E-Visits for 6 of the medical problems (excluding diarrhea and vaginal complaints) on days 1, 3, 7, and 14 following their E-Visit. We administered surveys in 4 domains: global assessment of improvement; health related quality of life; condition-specific symptom scores, and patient experience. We recorded any follow up care (within 21 day) regarding the initial E-Visit.

Over the first 3 months, 72 patients completed E-Visits; 61 were female with a mean age of 42 years old and 50 had a prior relationship with their E-Visit physician. The average wait time for a physician response to an E-Visit was 3.0 hours for patients with Monday-Thursday E-Visits (n=46) and 50 hours for patients with Friday E-Visits (n=5); 21 patients received no message response. There was an average of 1.75 messages between the physician and patient as part of the E-Visit. We interviewed 6 respondents. Respondents were generally satisfied with e-visits: 67% (4/6) were very satisfied; 83% (5/6) would use an E-Visit again; 83% (5/6) would recommend E-Visits to others; and 100% (6/6) thought that their E-Visit was very convenient.

E-Visit volume has been low during the first 3 months of availability at 2 primary care practices. Respondents who have completed E-Visits are highly satisfied with their care and are interested in using E-Visits in the future. E-Visits have the potential to enable practices to provide accessible, convenient urgent care that preserves primary care continuity.
Culturally Tailored Cooking and Nutrition Skills Workshops for Haitians in the Cambridge Area

Melanie Baskind
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Marie-Louise Jean-Baptiste, MD
Department of Medicine
Cambridge Health Alliance

In the context of the nation’s health crisis, minority and immigrant populations have disproportionately high rates of obesity, diabetes mellitus and other chronic conditions. Despite accounting for only 5% of Cambridge Health Alliance’s (CHA) primary care patients, Haitians make up 11% of its diabetes registry. While food and eating habits are known to be an important component of culture, weight loss interventions rarely take ethnicity into account.

Dr. Jean-Baptiste has run group diabetes meetings for Haitian patients at CHA for over ten years. In response to patient requests, and noting continued discrepancies between patient reported behavior and health outcomes, we asked whether culturally tailored cooking and nutrition skills workshops could help address health disparities in this community.

In this pilot study, we investigated the educational, social, behavioral, and clinical impact of a culturally tailored cooking intervention. Through qualitative methods we sought to understand the patient experience of the workshops and the barriers Haitians face in maintaining a healthy lifestyle in the US.

Twelve individuals with diabetes, hypertension, and/or obesity were enrolled, and six three-hour workshops were held between May and August, during which participants cooked and ate traditional, but modified, Haitian dishes together. Clinical data was recorded and each workshop had an interactive educational session. At-home interviews were conducted towards the end of the intervention, and on the final day participants completed an educational retention survey.

Of the five educational retention surveys collected, all subjects remained perfect or improved. While collection methods complicate statistical analysis, this indicates that this intervention may result in increased nutritional knowledge. PAM surveys (n=5) revealed an unexpected average decrease in PAM score of -7.6 points (95% CI -2.59, -12.6; p=0.0136), which requires further investigation but may indicate that this intervention revealed the complexity of effectively managing chronic condition in ways that were previously unknown. There was a non-significant weight gain (n=10) of 0.79 lbs/week (95% CI -0.062, 1.64; p=0.065), though there was wide variation and medication changes may have been confounding.

Qualitative interviews with nine participants indicate that culturally tailored workshops are a promising intervention for improving health in this Haitian community. Patients consistently reported cooking with less oil, less salt, and less sugar, and expressed enthusiasm for the classes. Financial stress, poor access to fresh and tasty food, and peer resistance to change were identified as ongoing challenges.

We acknowledge this is a pilot study with a small number of participants, and further research is needed to determine whether clinical and educational impact is statistically significant and sustained. Major limitations include lack of a control group and selection bias, as participants were recruited from Dr. Jean-Baptiste’s group diabetes meetings. As participants have been exposed to some of this information before, these results must be interpreted within the context of a longitudinal series of interventions. Whether or not this model may be effective for primary prevention also remains to be explored.
The role of Vascular Endothelial Growth Factor in intramembranous ossification during embryonic mandibular development

Seth Bradbury
Harvard School of Dental Medicine, William Bosworth Castle Society, Class of 2018

Bjorn Olsen, MD, PHD
Department of Developmental Biology, Olsen Lab
Harvard School of Dental Medicine

Vascular Endothelial Growth Factor A (VEGF) is involved in bone development and growth through stimulation of hypertrophic cartilage neovascularization as well as stimulating osteoblast proliferation during endochondral bone formation. In a recent publication, VEGF was proposed to play a role in intramembranous ossification of the jaw through stimulating growth of the mandibular artery. To determine this, the authors looked at the effect of conditionally knocking out VEGF in neural crest cells (NCC). The mandible develops first as a cartilaginous structure, Meckel’s cartilage, which is then surrounded by bone. Meckel’s cartilage and mandibular bone are NCC derived tissues, so these mice had reduced VEGF expression throughout the mandible. Mandibular artery growth was reduced in the mutants as was overall mandibular growth. Another group of investigators examined similar conditional VEGF mutant mice and found reduced ossification within the mandibles of mutant mice involving downregulation of BMP-2. We are further investigating the role of VEGF derived from different subpopulations of NCC within the developing mandible to see if there are effects independent of mandibular artery growth. We hypothesize that VEGF can act directly on osteoblasts to stimulate intramembranous ossification within the developing mandible.

Instead of knocking out VEGF in all NC-derived cells using Wnt-1-Cre, we investigate the effects of knocking out VEGF in subpopulations of NC-derived cells. Past studies have highlighted Col-2 expression as a marker of cartilage development (chondroblasts) and osterix expression as a marker of bone development (osteoblast progenitors). Therefore, with Osterix-Cre and Col-2-Cre mice with floxed(fl/fl) or wild-type VEGF alleles we can examine effects of VEGF in NC-derived subpopulations. We will compare percent change in mandibular length and width in E15.5 and P1 VEGFfl/fl;Osx-Cre mutants and control VEGF+/+;Osx-Cre mice. The same will be done with VEGFfl/fl;Col-2-Cre and VEGF+/+;Col-2-Cre mice to see if there is a significant difference in mandibular growth at these time points.

To investigate the role of VEGF without involvement of the mandibular artery, we will harvest embryos at E15.5 and remove mandibles to be grown in organ culture after removing surrounding vessels. We will study effects of VEGF and BMP-2 in these mandibles by treating some with exogenous VEGF or BMP-2. After culturing, we will assess all groups to see if there is a difference in growth based on length and width measurements of the mandibles. These experiments should reveal potential functions of VEGF in mandibular development independent from mandibular artery growth.
High-Value, Cost-Conscious Care in Medical Education

Eileen R. Brandes
Harvard Medical School, Francis Weld Peabody Society, Class of 2018
Fosters Scholar

Steven E. Weinberger, MD, FACP
Executive Vice President & Chief Executive Officer, American College of Physicians
Senior Lecturer, Harvard Medical School

Healthcare costs represent 18% of GDP and are continuing to rise. A major contributor is healthcare waste: the overuse and misuse of diagnostic testing and treatment. A recent approach to this problem is promotion of the concept of High-Value Care (HVC), i.e. healthcare that provides the greatest benefit relative to cost and harm. Although effecting a culture change about HVC has become a major priority in medical education, it is currently unknown to what extent HVC has permeated the curriculum of medical school and the clinical experiences of medical students. In this study, we developed a web-based survey of 18 questions to compare exposure and attitudes of medical students and residents to HVC. The survey was distributed to a random sample of 1000 second year medical students (M2), 1000 fourth year medical students (M4), 500 PGY2 and 500 PGY3 internal medicine residents (PG) who are members of the American College of Physicians. We received 479 completed questionnaires, yielding a 16% response rate, including responses from students in 144 allopathic or osteopathic medical schools.

Overall, 76% of respondents indicated that they had been introduced to the concept of HVC at some point during education or training and the percentage increased over the course of training (61% of M2, 79% of M4 and 88% of PG; p<0.05). However, only 29% of all respondents reported that they were either very or moderately familiar with HVC. At all stages of training, “fear of missing something” was felt to be the most important factor contributing to administration of relevant but unnecessary tests, followed by “wanting to be as thorough as possible.” There was a significant decrease over the course of training in considering “fear of a negative evaluation for not being thorough” as a major barrier to HVC (45% of M2, 31% of M4 and 23% of PG). Trainees with clinical clerkship experience (i.e. M4 and PG) reported the highest likelihood of exposure to HVC during their Internal Medicine Clerkship (89%), followed by Family Medicine/Primary Care (55%); all other clerkships had 30% exposure or less. All groups reported that lack of information about the “cost of a test or treatment” was the most important barrier for learning about HVC.

In conclusion, although HVC exposure increases during training, barriers remain to both learning about and practicing HVC. There is also a wide variation in exposure to HVC across different medical school clerkships.
The Yield of Subsequent Radiographs During Nonoperative Treatment of Radial Head and Neck Fractures

Kyle Renard Burton
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

David Ring, MD PhD
Hand and Upper Extremity Service, Department of Orthopedic Surgery
Massachusetts General Hospital

The value of radiographs subsequent to those used to diagnose an isolated radial head or neck fracture and select nonoperative treatment is uncertain. This study tested the null hypothesis that there are no patient, surgeon, or injury factors associated with alteration in patient management based on subsequent radiographs. Secondarily we tested the null hypothesis that the use of subsequent radiographs is not associated with patient, surgeon, and fracture characteristics.

We identified 415 adult patients with nonoperative treatments for isolated Broberg and Morrey modified Mason type 1 or 2 fractures at a large urban hospital system during years 2013 and 2014. Patient demographics, fracture characteristics, provider characteristics, and treatment details were obtained from a hospital database. One of 255 patients with 262 fractures that had subsequent radiographs (0.4%) was offered surgery, but declined. In multivariable analysis, displaced fractures were more likely to have subsequent radiographs but surgeon-to-surgeon variation was a far more influential factor.

Radiographs subsequent to diagnosis do not alter treatment of radial head fractures with no associated ligament injuries or fractures. The substantial surgeon-to-surgeon variation in the use of subsequent radiographs suggests that this may be a good focus for quality improvement initiatives.
Depression and Previous Malnutrition as Predictors of Breastfeeding Duration

Kia Byrd
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Janina Galler, MD
Chester M. Pierce Division of Global Psychiatry
Massachusetts General Hospital

Purpose: The effects of post-partum depression and mood on breastfeeding length have been extensively characterized in the literature, revealing that maternal depressive symptoms are significantly associated with reduced breastfeeding preference. However, few studies have examined the combined effects of both psychosocial factors and malnutrition during childhood/adolescence on breastfeeding and the effects among intergenerational cohorts in developing nations. This study seeks to explore the effects of adolescent depressive symptoms and childhood malnutrition on the duration of breastfeeding in the context of a developing Caribbean nation.

Methods: This was a retrospective cohort study undertaken using the Barbados Nutrition Study archival data set. The Child Medical Examination was used to ascertain demographic and ante- and postnatal characteristics from 23 Barbadian parent-offspring pairs. Incidence of parental depressive symptoms during adolescence was determined using the Minnesota General Adjustment and Morale Scale. The Zung Self-Rating Depressive Scale was used to assess depressive symptoms during adulthood. With respect to demographic information, nutritional status, and depressive characteristics, we used t-tests for continuous variables and chi-square or Fisher’s exact test for categorical variables to compare participants who reported breastfeeding duration ≥ 6 months with those who reported breastfeeding duration < 6 months.

Results: Among the sample population of parent-child pairs, a total of 16 pairs (69.6%) reported breastfeeding duration ≥ 6 months, and 7 pairs (30.4%) reported breastfeeding duration <6 months. Participant mothers who reported breastfeeding ≥ 6 months appeared less likely to experience medical problems during pregnancy (p=0.069). A larger percentage of mothers who breastfed their infants for < 6 months reported a history of malnutrition (80.0%) in comparison with mothers who breastfed for ≥ 6 months (33.3%). Furthermore, mean youth depression score in mothers breastfeeding < 6 months (-0.13 ± 2.92) was higher than in mothers breastfeeding ≥ 6 months (-0.51 ± 0.94). Nutritional history and depression scores, however, showed no significant association with breastfeeding duration (p=0.242; p=0.417).

Conclusions: Our study of small sample size illustrates trends (though non-significant) that may suggest a role of early childhood malnutrition and history of adolescent depressive symptoms in breastfeeding duration. Larger studies are recommended and necessary to establish a potential link between nutritional status, depressive symptoms, and breastfeeding duration.
Understanding Links between Childhood Adversity and Midlife Health Outcomes: A Longitudinal Study Across Generations

Christopher F. Calahan
Harvard Medical School, Francis Weld Peabody Society, Class of 2018

Robert J. Waldinger, MD
Director, Harvard Study of Adult Development
Department of Psychiatry, Massachusetts General Hospital

The psychosocial factors that contribute to healthy aging are not fully understood. While it has been shown that childhood trauma and adversity contribute to increased rates of depression, smoking, and poor mid-life health, there is still substantial room for progress in determining the mechanisms by which this link occurs1.

The Harvard Study of Adult Development at MGH has longitudinally followed a group of 724 men since the 1930s, collecting surveys every other year which capture metrics such as lifestyle, employment, relationships, home environment and self-reported health. The first-generation (G1) sample consists of 268 men recruited as Harvard College sophomores and 456 men recruited in adolescence from disadvantaged inner-city Boston families. Using data from the first generation cohort, this project aimed to examine family adversity thought to influence children growing up in these men’s homes.

Thirty-five G1 charts were reviewed throughout the summer, each with data about one participant’s family life spanning the 1940s to present day. For each G1 participant, data were collected on the environment in which their children (G2) were raised, between the date when the oldest child was born to the date that their youngest child turned nineteen years old. Childhood adversity was coded into nineteen different categories that were determined through an extensive review of the literature1,2. These categories included information on G1 marital status, mental & physical health, socioeconomic status, stressful transitions, abuse and more. The G1 subjects in this pilot study included 17 men from the cohort of Harvard College sophomores and 18 men from the inner-city cohort, in order to provide variation in SES and background.

Preliminary analyses will examine the correlation between G2 childhood adversity and midlife outcomes in both educational achievement and relationship status. The influence of G1 relationship status and educational achievement on G2 outcomes will be considered in these analyses. Secondary work will aim to normalize G1 socioeconomic status (SES) by tracking inflation and poverty data going back to the 1940s. This will allow for further investigation as to the role of SES in childhood adversity and long term outcomes. These analyses intend to contribute to the progress of the second generation study, which is about to begin recruiting G2 subjects for in-person physiological assessments of midlife health.
A prospective study of circulating anti-HLA antibodies in lung transplantation

Severine Cao
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Hilary Goldberg, MD
Lung Transplant Program, Department of Medicine
Brigham and Woman's Hospital

Antibody-mediated rejection (AMR) contributes to allograft dysfunction in kidney and heart transplant recipients, but its role in lung transplant recipients remains poorly defined. AMR is thought to be dependent upon the presence of circulating antibodies specific for the donor’s HLA (DSA) that mediate rejection via the complement cascade. AMR is increasingly recognized as a clinical entity that may contribute to allograft rejection in lung transplant recipients, but little is known about its features or pathogenesis in this population.

We performed a pilot study using a prospective cohort of patients listed for lung transplantation at our institution to investigate the prevalence of pre-transplant antibodies and their correlation with the incidence of post-transplant antibodies. Each candidate listed for transplant was tested for circulating class I (Cl) and class II (CII) anti-HLA antibodies/DSAs using the LABscreen® Single Antigen assay per clinical protocol. We defined antibodies as present if they were detected at a mean fluorescence intensity (MFI) above 1000 on the most recent pre-transplant serum sample or on at least two samples tested within 6 months before transplant. We then screened recipients at 1, 3, 6 and 12 months post-transplantation for anti-HLA antibodies/DSAs, using the same MFI threshold. We used descriptive statistics to calculate the prevalence of pre-transplant antibodies and the incidence of post-transplant antibodies.

Of the ten patients enrolled to date, six had pre-transplant antibodies at MFI>1000. Of these six, two (33.3%) had antibodies against both CI and CII, three (50%) had antibodies against CI only, and one (16.7%) had antibodies against CII only. Only two out of ten patients (20%) had pre-transplant DSAs. Within a year post-transplantation, five patients (50%) had post-transplant antibodies at MFI=1000. Two of these patients (40%) had antibodies against both CI and CII, one (20%) had antibodies against CI only, and two (40%) had antibodies against CII only. Three of the five (60%) antibody profiles detected post-transplantation were similar to those found pre-transplantation. None of the antibodies detected post-transplantation was donor-specific.

Our results confirm prior data suggesting that most antibodies detected before transplant are specific for CI, whereas most antibodies detected post-transplant are specific for CII. We also report an early finding that a majority of the antibody profiles detected post-transplantation correlate with profiles detected pre-transplant.

In future analyses, we hope to assess the statistical significance of the development of post-transplant anti-HLA antibodies/DSA, and to determine the antibody profile most clearly associated with the development of AMR.
Quantifying the gender difference in radiation risk from lung cancer screening and follow-up: A mathematical modeling study

Emmanuel Carrodeguas
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Chung Yin Kong, PhD
Associate Professor of Radiology, Harvard Medical School
Senior Scientist
Massachusetts General Hospital Institute for Technology Assessment

Lung cancer is a significant public health problem, and while prognosis is often poor, early detection can increase survival. Based on findings regarding the effectiveness of lung cancer screening using low-dose Computed Tomography (LDCT) (~20% mortality reduction), the Center for Medicare Services (CMS) has released a memo covering screening up to age 77. While benefits from screening are undeniable, CT exams can expose patients to radiation, inducing cancers that temper this benefit.

Computational modeling can be used to better characterize these effects, especially for the characterization of gender differences in radiation risk. This is significant for guiding the refinement of screening protocols, as epidemiological studies have shown that females are at higher risk for radiation-induced cancers due to increased radiosensitivity.

In this study we combined the Massachusetts General Hospital’s Lung Cancer Policy Model (LCPM) and the radiation risk model from the Committee on the Biological Effects of Ionizing Radiation VII (BEIR VII) report to estimate the benefits and the numbers of radiation-induced cancers among male and female patients from screening and follow up radiation, varying stopping age of screening, radiation dose, and nodule follow-up protocols (Fleischner Society and Lung Imaging Reporting and Data System (LungRADS)).

Without accounting for radiation-induced cancers, male and female cohorts showed similar mortality reduction in screened groups over non-screened groups (21.4% in females to 21.6% in males (\( \Delta 0.2\% \))). Considering radiation-induced cancers however, the female cohort had a higher mortality reduction (19.8% in females to 19.4% in males (\( \Delta 0.4\% \))). Females had a higher burden of radiation-induced cancer mortality (55.3/100,000 in females to 48.2/100,000 in males), with higher rates of lung, breast and stomach cancer. The majority of radiation-induced cancers in females were due to follow up radiation (53.7% of radiation-induced cancers), as opposed to due to screening radiation in males (57.6% of radiation-induced cancers). Increasing radiation-induced end-screening age to 80 reduced mortality by an added 0.4-0.5% in both males and females, with 0.2-1.0/100,000 added induced cancer deaths. With regards to follow-up protocols, the Fleischner Society guidelines resulted in a 9.2 to 9.5 fold increase in radiation-induced cancer mortality and incidence over the LungRADS guidelines.

Altogether, screening can be effective in reducing mortality for both genders, but the numbers of radiation-induced cancers are higher among females than males. Furthermore, the LungRADS follow-up protocol resulted in less radiation-induced cancers over the Fleischner Society guidelines. Our results highlighted the importance of balancing radiation-risk and screening benefits, especially in the female cohort.
Imaging Patterns Predict Survival in Recurrent Glioblastoma Patients Treated With Bevacizumab

Ken Chang
Harvard Medical School, Irving M. London Society, Class of 2018

Patrick Y. Wen, MD
Center for Neuro-Oncology
Dana-Farber Cancer Institute

Glioblastoma is the most common primary adult brain tumor and carries one of the worst prognoses amongst human cancers. Patients with recurrent GBM have a dismal prognosis, with a median survival of just 25-40 weeks. Bevacizumab is a humanized antibody against vascular endothelial factor approved for treatment of recurrent glioblastoma. While this therapy has resulted in a significant treatment response rate in a subset of patients with recurrent glioblastoma, its overall survival benefit is modest at best. There is a need to discover imaging biomarkers that can aid in the selection of patients who will most likely derive survival benefit from bevacizumab.

In this study, we retrospectively examine MRI studies of 126 patients with recurrent glioblastoma before and within 3.5 months following bevacizumab treatment initiation. We hypothesize that multi-modal imaging feature extraction combined with machine learning algorithms provide more accurate survival prediction compared to the standard radiographic assessment based on the Response Assessment in Neuro-Oncology (RANO) Criteria. A total of 2297 features were extracted from pre-contrast T1W, T2W, Apparent Diffusion Coefficient (ADC) map, and post-contrast T1W sequences. Patients were randomly assigned to either the training cohort (n=101) or the testing cohort (n=25). Support Vector Machine (SVM), a supervised learning model, was used to construct two classifiers: SVM_S to identify short-term survivors (survival time less lower third tile) and SVM_L to identify long-term survivors (survival time longer than upper third tile).

In the testing patient cohort, the average classification accuracy of SVM_L was 0.80 (AUC = .81) while the average classification accuracy of SVM_S was 0.64 (AUC = .81). The hazard ratio of short-term survivors to long-term survivors was 5.5 (p<.05) in the testing cohort. In contrast, the hazard ratio of progressors vs. no progressors based on RANO criteria at post-treatment imaging was 3.4 (p<.001) for all patients. These findings indicate that machine learning approach to analyze multi-modal MRI data improve prediction of survival outcome for patients with recurrent glioblastoma treated with bevacizumab.
Barriers to Accessing Care: Understanding Nonattendance Among Spanish-Speaking Patients

Carolina Chiou
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Arash Mostaghimi, MD, MPA
Department of Dermatology
Brigham and Women's Hospital

Healthcare disparities disproportionately affect minority populations. One barrier to care is language: patients who do not speak English may have more difficulty in navigating the healthcare system. Despite efforts to improve access for patients, the rate of Spanish-speaking patients who miss appointments (non-attendance) remains high. The goal of this study is to use structured interviews of Spanish-speaking patients with non-attendance to identify barriers to receiving care.

This study was performed at the Brigham and Women’s Department of Dermatology at the Brigham and Women’s Hospital. We identified Spanish-speaking patients who missed appointments from May to July of 2015. These subjects were contacted via telephone, in Spanish, and asked to voluntarily participate in a recorded structured interview. We made a minimum of three attempts to contact patients. A total of 134 patients were contacted, 49 participated and 85 either did not answer or declined to participate. Interview questions consisted of both open and close ended formats, and explored the patients’ reasons for nonattendance and their relevant experiences with the hospital. The data collected was transcribed and coded to identify common themes.

Preliminary evaluation of the data demonstrates that reasons for nonattendance are largely heterogeneous and are attributable to both structural and external factors. We identified three major themes in regards to structural barriers: 1) The high cost of parking at the hospital (or limited options for free parking), 2) inadequacies in the appointment reminder system related to the language and timing used, and 3) difficulty navigating the system due to a lack of Spanish-speaking personnel. Further analysis needs to be completed to confirm these findings and discern subthemes.

Limitations to this study include a small sample size and a potential for selection bias among patients who chose to participate in the study. In addition, this study was limited to dermatology patients, and interdepartmental differences may restrict the results from applying more broadly. For instance, the appointment reminder systems may be operated differently and the number of Spanish-speaking personnel may vary. Therefore, a more comprehensive approach including different departments within the hospital may provide information on whether the results represent institution wide barriers. In addition, comparing data for individual departments may prove useful in identifying best practices.
Optimizing Protocols to Rule-Out Central Line-Associated Bloodstream Infections in Pediatric Patients Receiving Home Parenteral Nutrition

Bennet Cho
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

Mark Puder MD, PhD
Department of Surgery, Boston Children’s Hospital

Intestinal failure (IF) is defined as the inability to absorb nutrients enterally due to insufficient bowel length or absorptive capacity. In pediatric patients with IF, parenteral nutrition (PN) is a lifesaving therapy that is administered intravenously through a central venous catheter (CVC). However, long-term indwelling CVCs can transmit infectious agents from the skin to the bloodstream, resulting in central line-associated bloodstream infections (CLABSI). Catheter-related sepsis is a leading cause of morbidity and mortality in patients receiving home PN (HPN), yet currently, there is no data-driven standard of care defining optimal hospitalization duration to rule-out CLABSI in this population.

At Boston Children’s Hospital, HPN patients with suspected CLABSI are admitted for 48 hours of monitoring and empiric antibiotics. Patients may be discharged if blood cultures are negative for infection after 48 hours. A survey administered to 42 pediatric HPN programs across the United States demonstrated that most responding programs use a 48-hour admission protocol to rule-out CLABSI despite a lack of evidence to support this practice. The goal of this study is to determine an optimal length of inpatient admission for patients who present for CLABSI evaluation.

Our previous retrospective study demonstrated that positive blood cultures in pediatric HPN patients become positive within 24 hours. Based on this, we hypothesize that a clinically significant majority of pediatric IF patients with CLABSI develop positive blood cultures within 24 hours and that a 24-hour admission to rule-out CLABSI may be as safe and effective as a 48-hour admission.

This is a 2-year prospective observational study of pediatric IF patients with an indwelling CVC for PN delivery who are admitted to the hospital to rule-out CLABSI. The primary endpoint is time to positive blood cultures in patients with CLABSI. Data collected for all patients include laboratory values, physical exam findings, symptoms, antibiotics administered, and costs and charges for each admission. Data accrued may guide appropriate length of admission to rule-out CLABSI. Additional goals include identifying features that correlate with delayed time to positive blood cultures and circumstances in which a 24-hour admission is not sufficient to rule-out CLABSI.

Identifying a safe length of stay for CLABSI evaluation and markers to guide risk stratification may allow institutions to establish a data-driven standard of care for ruling out CLABSI that maintains maximal efficacy and minimizes inpatient days, unnecessary doses of antibiotics, exposure to nosocomial infections, and financial burden for patients and the healthcare system.
Evaluating the Implementation and Management of a Task-Sharing Strategy for the Integration of Mental Health and HIV/AIDS Care in Tanzania

Stephanie Choi
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Mary Smith Fawzi, ScD
Department of Global Health and Social Medicine
Harvard Medical School

The co-morbidity of HIV/AIDS and mental disorders poses a significant problem in resource-limited settings. The Tanzanian government recently revised their health policy goals to emphasize the integration of mental health and HIV care, but limited evidence exists on how such integration can be done successfully. Task-sharing, or the involvement of non-specialist health workers to deliver psychological treatment, has been demonstrated as a promising approach to address the existing shortage of mental health professionals. A cluster randomized controlled trial was recently launched in Tanzania to evaluate a community health worker (CHW) facilitated intervention with problem solving and cognitive behavioral therapy components for the treatment of depression among perinatal women living with HIV.

This qualitative study was carried out within the context of the randomized controlled trial and aimed to understand from the perspective of CHWs their involvement and contributions to mental health care, the obstacles they face in facilitating group counseling sessions, and potential barriers to scale-up. A total of 21 semi-structured individual in-depth interviews were conducted from July-August 2015 with the use of an interpreter. The interviews were audio-recorded, transcribed, and coded through a process based on Grounded Theory. A limitation to this study is that it only provides a snapshot of the experience of the CHWs since the randomized controlled trial will continue through 2017.

The group of community health workers trained to deliver group psychotherapy consists entirely of HIV-positive women with basic primary or secondary school education. None of these women had prior experience working as community health workers or counselors, though many were involved in HIV support groups. These CHWs serve a unique role within health care system because unlike traditional health providers, these women share similar experiences with their patients and such empathy enables them to gain the patient trust critical in the treatment of HIV/AIDS and depression.

Data analysis reveals the CHWs to be driven by an innate sense of volunteerism and a desire to empower other women living with HIV, as well as a desire to further their own education. While monetary compensation is appreciated, it is not the primary motivating factor. A major challenge CHWs face in delivering group psychotherapy is high illiteracy rate and low comprehension among their patients, in addition to a lack of material resources for teaching. Supervision is viewed as necessary component of each group session and the low supervisor to CHW ratio allows for individual attention and feedback.
Deficits of Language, Speech and Writing in Idiopathic Normal Pressure Hydrocephalus

Esther H. Chung
Harvard Medical School, Francis Weld Peabody Society, Class of 2018

Mark D. Johnson, MD, PhD
The Adult Hydrocephalus Program, Department of Neurological Surgery
Brigham and Women’s Hospital

Idiopathic Normal Pressure Hydrocephalus (iNPH) is a disorder of unknown etiology characterized by gait instability, incontinence and dementia. The symptoms can be ameliorated by shunt placement for cerebrospinal fluid (CSF) drainage, but the causes of shunt-responsive iNPH are unknown. Anecdotal reports suggest the presence of impairments in word-finding and other aspects of language. The objective was to specifically determine the prevalence and nature of language and speech difficulties in iNPH and whether these deficits improve after CSF drainage. We reviewed the medical records of 529 patients who underwent shunt placement for iNPH at our institution between July 2001 and March 2015. Detailed information was obtained from clinic notes and formal pre- and post-operative neurocognitive evaluations.

Analysis of 98 prospectively performed pre-operative neurocognitive evaluations revealed verbal fluency impairments in 66.3% of patients. In retrospective analysis of all 529 patients, language deficits were identified in 21.7%, with 93.0% demonstrating expressive and 22.6% demonstrating receptive language deficits. Among patients with expressive language deficits, word-finding difficulties were present in 43.9%. Verbal fluency impairments were present in 29.0% of this subgroup. Motor-related speech disorders were found in 12.9% of all patients. The most common motor-related speech difficulties included dysarthria (25.0%), overall slowness (27.9%), and stuttering (10.3%).

We performed a focused analysis of 13 iNPH patients who underwent both pre- and post-operative neurocognitive evaluations. Overall, 61.5% of patients experienced improvement in speech or language after shunt placement. About 31.0% demonstrated significant improvement in verbal fluency, while 7.7% declined. Approximately 23.1% of patients showed significant improvement in verbal learning, while 7.7% declined. 38.5% of patients demonstrated significant improvement in verbal retrieval and memory, while 7.7% declined. Roughly 31.0% demonstrated significant improvement in fine motor coordination, while 7.7% declined. Two of the 13 patients, one of whom improved, had neurocognitive symptoms characteristic of Alzheimer’s disease.

Our study is the first to demonstrate language and speech difficulties in up to 66.3% of patients with iNPH. Thus, the presence of such difficulties is not a negative predictor of disease. Nearly 62% of iNPH patients experience improvements in speech or language after shunt placement. Together, these data indicate that deficits in speech and language are integral components of iNPH pathology.

Primary limitations of this study are the limited number of patients with formal pre- and post-operative neurocognitive examinations, as well as the retrospective nature of the review of the larger group of 529 patients, which could introduce selection or information bias.
Mapping Childhood Malnutrition in Chiapas, Mexico

Maggie Cochran
Harvard Medical School, Francis Weld Peabody Society, Class of 2018

Patrick Elliott MD, MPH
Clinical Director, Compañeros En Salud – Partners In Health Mexico
Associate Physician, Division of Global Health Equity, BWH
Instructor in Medicine, Harvard Medical School

Chiapas is one of the poorest and most isolated states in Mexico, ranking last in the country on a number of socioeconomic indicators including income and health. In 2012, Compañeros En Salud (CES, a sister organization to Partners In Health) began providing high-quality, primary health care to the region. Recently, health care workers in the CES clinics have noticed an increase in children suffering from severe malnutrition. This change may be related to a fungal infestation that has led to shortages in local coffee production.

This project has three specific aims: (1) Determine the point prevalence of chronic malnutrition (stunting) and acute malnutrition (wasting) in children under five in the Chiapas communities that CES serves; (2) Compare these rates to the rest of Chiapas and to the rest of the country; (3) Use GIS-mapped prevalence data in order to generate hypotheses for future interventions and studies.

The study design for this project is a simple, cross-sectional survey. I traveled from home to home to perform a full census of four different communities. At each home, I measured the weight-for-height of each child under five (an indicator for wasting) and the height-for-age of each child under five (an indicator for stunting). I also surveyed the parents on a small number of socioeconomic and health-related questions so as to obtain a richer understanding of these children and families. I then plotted each household on a handheld GPS device. In total, I visited 294 houses and measured 428 children.

A preliminary data review has uncovered the following results: on average, 32% of children under five in the communities surveyed suffer from moderate-to-severe stunting, and 1.7% of children suffer from moderate-to-severe wasting. This is compared to an average of 31% of children suffering from stunting and 3.7% of children suffering from wasting in all of Chiapas, and 13.6% of children suffering from stunting and 1.6% of children suffering from wasting in all of Mexico. This fall I will complete the analysis of our measurement, survey, and location data. We will be using QGIS software for both mapping and statistical analysis, with the goal of designing targeted interventions based on our results.

A limitation to this study was the inability to interview every family in every community. Often, families were traveling and away from their home during the time that I was performing interviews; I was thus unable to obtain data from these unavailable families.
Characterizing the interactions of Bcl11a and Mammalian SWI/SNF (BAF) Chromatin Remodeling Complexes

Dawn E. Comstock
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018
Alexandra J. Miliotis Fellowship in Pediatric Oncology

Stuart H. Orkin, MD
Department of Pediatric Oncology
Dana Farber Cancer Institute and Boston Children’s Hospital

Bcl11a, a zinc finger transcription factor, is a critical regulator of hemoglobin switching and fetal hemoglobin (HbF) silencing. Deletion or inhibition of Bcl11a has been proposed as a potential therapy to reactivate HbF for the treatment of sickle cell disease and β-thalassemia. Further elucidation of the mechanisms of how Bcl11a achieves HbF silencing would facilitate design of targeted therapies for these diseases. Previous studies have implicated SWI/SNF complex subunits as potential Bcl11a partners. The goal of this project is to determine whether the interaction between Bcl11a and SWI/SNF plays an important role in fetal hemoglobin suppression.

We validated the interaction between Bcl11a and Brg1, a SWI/SNF subunit, using co-immunoprecipitation (Co-IP). In addition, we analyzed genomic co-localization of Bcl11a and Brg1 using chromatin immunoprecipitation followed by sequencing (ChIP-Seq). Finally, we assessed the functional roles of SWI/SNF subunits in hemoglobin expression using CRISPR/Cas9-mediated gene deletion.

Immunoprecipitation using biotin-tagged Bcl11a demonstrated binding interactions between Bcl11a and Brg1. For ChIP-Seq we tested several Bcl11a antibodies in mouse erythroleukemia (MEL) cells and identified Bcl11a binding sites at the genomic level. To further validate these Bcl11a localizations, we extended our studies to other cell types including pre-B cell lines and primary B cells, which allowed us to compare Bcl11a peaks between tissue types. Motif analysis suggested some additional factors might cooperate with Bcl11a for gene regulation. The functional consequences of these binding sites are being examined. To assess functionally whether certain SWI/SNF subunits are required for HbF silencing, we generated MEL cells deficient in subunits of the SWI/SNF complex including Brg1, Baf155, Baf170 and Baf250a, using CRISPR/Cas9-mediated gene deletion. The preliminary results suggest that these subunits of the SWI/SNF complex are dispensable for hemoglobin silencing and are not essential in hemoglobin suppression in either induced or non-induced MEL cells, which is in sharp contrast to the essential role of Bcl11a in HbF silencing.

In summary, we have successfully performed Bcl11a ChIP-Seq, identified several novel Bcl11a binding sites, and started to assess the functional role of SWI/SNF in mediating HbF silencing. Further studies are necessary to determine whether other SWI/SNF subunits act in a redundant manner in hemoglobin regulation and to determine if these interactions are functionally relevant in other cell types. In addition, it is of interest to determine whether the Bcl11a-containing complex undergoes subunit switching during fetal-to-adult transition in erythroid development to discover additional factors that might contribute to HbF silencing.
Examining the Value of MRI in the Initial Management of Patients with Suspected Rotator Cuff Tears

Alejandro Cortes
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Scott D. Martin, MD
Department of Orthopedic Surgery
Brigham and Women's Hospital

Shoulder pain is one of the most common musculoskeletal concerns driving patients to seek medical help. Of these episodes, up to 70% can be accounted for by lesions of the rotator cuff — a confluence of four tendons deriving from the supraspinatus, infraspinatus, teres minor, and subscapularis muscles. The high incidence and crippling effects of rotator cuff tears (RCTs) impose a substantial health and economic burden to society.

Present diagnostic standards for patients with suspected rotator cuff pathology call for MRI of the symptomatic shoulder after physical examination. The purpose of this study was to examine the value of MRI in the initial management of patients in which RCTs were suspected, yet strength testing showed no major deficits. We also sought to characterize the demographics of the population under study.

All patients included in this prospective study completed a subjective shoulder questionnaire and history. Patients underwent standardized physical examination as well as strength and range of motion measurements of the shoulder (performed by a single board-certified orthopedic surgeon). Inclusion criteria included: chief complaint of shoulder pain, strength test minimum of 5-, no inciting traumatic event to either shoulder, screening radiographs and MRI of the symptomatic shoulder, 18 years or older, signed informed consent, ≥4 months or more of follow-up, and recommended conservative treatment post-examination. Demographic data and imaging results were collected through chart review.

80 patients, collected throughout a 15 month period, met the inclusion criteria. 63 patients (78.75%) with an average follow-up of 8.8 months (SD = 2.9, R = 4-14) did not seek surgery after conservative management was recommended, while 17 patients (21.25%) with an average follow-up of 8.5 months (SD = 3.3, R = 4-14) did. This suggests that 63 people had premature MRIs (did not assist in preoperative planning), and an economic burden of $263,403 could have been saved ($4,181/MRI).

The overuse of MRI observed in this study and the high economic cost of MRI in the preoperative management of RCTs provide a strong case for the reevaluation of the value of MRI in the initial management of patients where RCTs are suspected, yet strength testing showed no major deficits.
Clinical features associated with aggressive phenotype among immunohistochemically confirmed atypical adenomas

David James Cote
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2019

Edward R. Laws, Jr., MD
Department of Neurosurgery
Brigham and Women’s Hospital

In 2004, the World Health Organization (WHO) defined a new category of pituitary adenomas, known as atypical adenomas, to distinguish lesions with a high propensity for local recurrence and metastasis. These adenomas—defined as those with pathologically proven p53 immunoreactivity, a MIB-1 proliferative index greater than 3%, and increased mitotic activity—were aimed to serve as intermediaries between more common benign adenomas and rare pituitary carcinomas. Despite this pathological diagnosis, not all atypical pituitary adenomas display clinically aggressive behavior, defined as local recurrence despite medical, surgical, or radiosurgical treatment. The aim of this study was to determine factors that predict a clinically aggressive phenotype among a cohort of atypical pituitary adenomas.

Medical records from Brigham and Women’s Hospital were retrospectively reviewed from April 2008 to July 2015 for all patients surgically treated for atypical adenomas as defined by the WHO criteria. Relevant variables, including demographic data, past medical history, endocrine outcomes, preoperative and postoperative MRI findings, clinic notes, and intraoperative findings were collected. Clinically aggressive adenomas were defined as occurring in those patients who necessitated additional therapeutic intervention after the index surgery, including additional surgery, medical therapy, or radiosurgery.

Forty-seven patients with immunohistochemically confirmed atypical adenomas were identified and of these, 23 were noted to have a clinically aggressive course. Among the remaining 24 patients, the disease remained silent after the index surgery. The two groups were well matched with regard to age, gender, preoperative symptoms and past medical history (p > 0.10). On univariate analysis, clinically aggressive lesions were more likely to have a larger axial diameter on MRI (2.9 ± 1.9 vs. 1.9 ± 0.7, p = 0.02), greater incidence of cavernous sinus invasion (65% vs. 20.8%, p < 0.01), and greater incidence of clival extension (60.9% vs. 0%, p < 0.01) on preoperative imaging. The two groups were equivalent with regard to immunohistochemical staining of all anterior pituitary hormones. Clinically aggressive lesions, however, had a higher average MIB-1 proliferative index (7.7% ± 4.9 vs. 5.3% ± 2.9, p = 0.03). On multivariate analysis, the MIB-1 proliferative index trended towards statistical significance (p = 0.06) as an independent predictor of clinical aggressiveness.

Atypical pituitary adenomas demonstrate increased numbers of mitotic figures on histopathology, but not all necessary demonstrate an aggressive clinical phenotype. Predictors of aggressive clinical course based on these data include cavernous sinus invasion, larger axial diameter on MRI, and clival extension.
Atrial fibrillation (AF) is the most common significant cardiac arrhythmia and the strongest common risk factor for ischemic stroke. It increases stroke risk 5-fold and accounts for 15% of all strokes in the United States. Warfarin anticoagulation can largely prevent AF-associated thromboembolic events, but increases bleed risk. Frequent testing with dose adjustment is needed to maintain INR levels in the therapeutic range. Novel anticoagulants (NOACs) now challenge warfarin as primary stroke-preventive therapy for AF. While available at fixed doses, they are costlier to patients.

Time in the therapeutic range of INR 2.0-3.0 (TTR) is the primary means of assessing quality of warfarin therapy. Secondary analyses of randomized trials indicate that warfarin has comparable efficacy and safety as NOACs at TTR ≥70%. It is unclear whether AF patients with TTR ≥70% will remain stably anticoagulated and avoid the need to switch to a NOAC. We assessed stability of warfarin anticoagulation in AF patients with an initial TTR ≥70%.

Our study utilizes ATRIA, a large community-based cohort of newly diagnosed AF patients receiving care at Kaiser Permanente of Northern California. We identified 2521 new warfarin users who continued therapy over 15 months. Months 1-3 were excluded to achieve initial stable warfarin dose. For patients with TTR1 (months 4-9) ≥70% (TTR determined by the Rosendaal interpolation method), we described the distribution of TTR2 (months 10-15) and assessed multivariable (logistic regression) correlates of persistent TTR ≥70%.

Of 1074 patients with TTR1 ≥ 70%, 57% (95% CI: 53-61%) persisted with TTR2 ≥ 70%. Only 15% (13-17%) deteriorated to a TTR2 < 50%, considered to be poor warfarin therapy. In multivariate analyses for persistence, two clinical features independently predicted TTR2 ≥70%: TTR1 ≥ 90%, aOR [95% CI]: 1.43 [1.05,1.93]; and heart failure, aOR: 0.78 [0.57, 1.06].

Altogether, we found that nearly 60% of AF patients with high-quality initial 6-month TTR on warfarin will maintain TTR ≥70% over the next 6 months. A minority deteriorate to very poor TTR. Patient features do not strongly predict deterioration. Our analyses considered only patients who newly and continuously took warfarin over 15 months in order to compare initial and subsequent period TTRs. Patients who halted warfarin in the second period were not included. Overall, our study supports watchful waiting for AF patients with initial high-quality warfarin anticoagulation before switching to a costlier NOAC.
Development of a Smart-Phone based Application to Estimate Repolarization Alternans

Steven Dalvin
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Antonis A. Armoundas, PhD
Cardiovascular Research Center, Massachusetts General Hospital

Sudden cardiac death (SCD) is one of the leading causes of death in the United States, claiming over 200,000 lives each year. It has been demonstrated that repolarization alternans (RA), an every other beat fluctuation of the ST segment or T-wave in an electrocardiogram, has been associated with increased risk of SCD via ventricular tachycardia (VT) or ventricular fibrillation (VF). Therefore, continuously monitoring RA in vivo will enable monitoring and assessment of a patient’s risk of SCD and may help guide treatment. However, no such device is currently available. Thus, we aimed to develop a Smart-Phone based monitoring system to estimate RA in ambulatory subjects and validate this system in a myocardial infarction swine animal model.

Several steps towards developing this novel system were taken prior to this work, including development and validation of the Smart-Phone based ECG acquisition hardware and the RA estimation algorithm in MATLAB. Using the MATLAB RA estimation algorithm as a guide, an RA estimation application was developed in Java (the programming language Android Smart-Phones utilize), with changes made as necessary to accommodate a Smart-Phone platform. To estimate RA, a spectral analysis of the ST segment and T wave portions of the ECG signal was performed. Using the power spectrum, a statistical measure of the significance of RA was then calculated.

We are nearing completion of the RA estimation algorithm in Java. We are validating the algorithm on a desktop computer by comparing the results it produces to those produced by the previously validated MATLAB algorithm. Once validation is complete, we will make the minor changes necessary to run the algorithm on a Smart-Phone, which will utilize a previously developed and tested ECG-acquisition system. We will then validate this completed system in a myocardial infarction swine animal model.

We are confident that we will be able to successfully complete our Smart-Phone based RA estimation system. Continuous monitoring of RA will help assess a patient’s risk of SCD, may improve disease prevention, and may guide treatment. Furthermore, improving accessibility to RA detection and monitoring may help guide our understanding of RA and refine its predictive capacity to even greater diagnostic capability.
Effect of Social Media on Dissemination of Preventive Oral Health Measures Through Accessible Online Learning Modules in Rwanda

Lindsay D’Amato
Harvard School of Dental Medicine, Francis Weld Peabody Society, Class of 2018

Brittany Seymour, DDS MPH
Oral Health Policy and Epidemiology
Harvard School of Dental Medicine

Around the world, society is facing revolutionary technological advances and globalization, permitting rapid information transfer. With the evolving technological landscape, media modalities are having a new and emerging impact on health through influencing individual health behaviors, policy decisions, foundation funding, and programs.

These programs can be especially useful in disseminating information in areas where there is a paucity of healthcare providers, such as in Rwanda, where there are no rural dentists and around 35 dentists for the entire country of nearly 12 million, a shockingly low number to adequately provide quality dental care. Further, Rwanda’s new president – deemed the “digital president” – has worked with the Rwandan government to advocate the use of social media in the realm of promoting good governance and service delivery.

With that in mind, we worked with students and faculty from the University of Rwanda School of Dentistry to develop the aims of the project, which were: first, to create specific, culturally sensitive objectives for an accessible series of preventive, educational oral health modules in Rwanda, and second, to translate the objectives into an online learning module that is linked to the University of Rwanda website, as well as larger social media outlets such as Facebook and Twitter.

Throughout seven weeks working with a team of students from the School of Dentistry in Kigali, Rwanda, we created educational modules in both English and Kinyarwanda, which included a medley of interactive features including games, videos, and audio clips. The first section of the module connects the relevance of oral health to overall health, emphasizing the importance of good oral health, and shows the consequences of oral disease. The second section presents maintenance of good oral health through basic oral hygiene techniques. The third section gives instruction on the importance of healthy nutrition on oral health. The fourth section introduces the role of dental therapists and dental surgeons in Rwanda, and the module ends with a summary of the main concepts.

Our module is to be published on the University of Rwanda’s website, shared on social media, as well as broadcasted across the patient waiting rooms at the medical facilities there, with a broader dissemination plan in the works for the future. Limitations encountered included learning the technological skills necessary to create the interactive modules, understanding terms and practices in oral hygiene in the Rwandan culture, and language barriers while working with our partners in Rwanda.
Use of Oblique Back-illumination Microscopy to image cellular interactions through Blood Flow

Paul Dannenberg
Harvard Medical School, Irving M. London Society, Class of 2018

Guillermo Tearney, MD, PhD
The Wellman Center for Photomedicine,
Massachusetts General Hospital

The ability to image cellular interactions under conditions of blood flow represents an important step towards understanding the pathogenesis of a variety of conditions. Transplant rejection, leukocyte adhesion deficiency, atherosclerotic disease and disorders of hemostasis all develop under such conditions. In this setting, morphological imaging analysis is usually performed using standard transmission Zernike or differential interference contrast microscopy. However, both these techniques have limited performance when imaging through whole blood, which is both highly scattering and absorbing.

Oblique back-illumination microscopy (OBM) uses a geometrically oblique light source to trans-illuminate the focal plane with a pair of fiber-coupled LEDs. We hypothesized that this illumination geometry would allow us to obtain high quality cellular images, even through thick layers of flowing blood. In our experimental setup, the optical fibers were positioned using a 3D printed holder, allowing us to easily vary the illumination angle and the distances between the fibers. We used the detection optics of a Leica inverted microscope to gather both Zernike and OBM images for the purpose of comparison.

Mouse fibroblast cells were cultured and plated into microchannels (Ibidi GmbH) ranging in heights of 100 to several hundred microns. Syringe pumps (New Era Pump Systems, Inc.) were then used to flow heparinized porcine blood over a monolayer of these cells at a constant flow rate of 0.015 µL/min. Three separate wavelengths of OBM illumination were used (660- , 780- , and 850-nm) and inter-fiber distances were varied between 8- and 14-mm. Incidence angles were also varied between 20 and 50 degrees from the sample plane. Investigation regarding the optimal geometric setup is still ongoing.

Our study confirmed that even at microchannel depths of just 100 microns, Zernike exhibited low phase-sensitivity and was unable to produce high contrast imaging due to the large amounts of scattering and absorption by red blood cells. By contrast, OBM was capable of high resolution, high phase-gradient contrast images, revealing clear subcellular structures of the fibroblasts despite the presence of blood flow. Our results suggest that OBM could be a useful research tool for monitoring cellular interactions under physiological blood flow conditions.
Tube Thoracostomy for Traumatic Hemothorax: Are We Too Eager to Intervene?

Leah Demetri
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Marc A. de Moya, MD
Division of Trauma, Emergency Surgery and Surgical Critical Care, Department of Surgery, Massachusetts General Hospital

Previous research has suggested that hemothoraces >300cc mandate TT. However, some patients with hemothoraces >300 cc may be appropriate candidates for observation. We therefore assessed the intervention patterns and outcomes for patients with traumatic hemothorax to determine whether hemothoraces >300ccs can be safely observed.

The 2000-2013 institutional trauma registry at a tertiary care, Level I Trauma Center was queried to identify all patients with traumatic hemothorax. Hemothorax size was defined by hemothorax volume according to the previously validated formula $V = d^2 * L$, where $d$=greatest depth of the hemothorax and $L$=total craniocaudal length occupied by pleural fluid. Patients who did not receive a chest CT scan or received TT prior to CT were excluded. Hemothorax size was categorized into “small” (<300cc), moderate (>=300 and <900cc), or large (>=900cc) groups. Intervention patterns and outcomes were categorized as: “early TT” (TT <24hr after CT), “successful observation” (neither TT nor surgical intervention), or “failed observation” (TT nor surgical intervention >24hr after CT). Univariate analyses assessed differences in intervention patterns and outcomes between hemothorax size groups. Multivariate analyses were performed to determine the impact of hemothorax size on the likelihood of successful observation, controlling for ISS.

193 traumatic hemothoraces were identified and 102 hemothoraces met inclusion criteria; 36 (35%) were small, 27 (26%) were moderate, and 39 (38%) were large. 83% (30/36) of small hemothoraces and 81% (22/27) of moderate hemothoraces were initially observed without early TT; of those, moderate hemothoraces were successfully observed as often as small hemothoraces [68% (15/22) vs. 77% (23/30), $p=0.50$]. In contrast, only 64% (25/39) of the large hemothoraces were initially observed without TT, and of those, significantly more failed observation compared with moderate hemothoraces [68% (15/22) vs. 16% (4/25), $p<0.001$]. On multivariate analysis, moderate hemothoraces were statistically as likely as small hemothoraces to be successfully observed [OR 0.68, 95% CI 0.19-2.38, $p=0.543$], whereas large hemothoraces were much more likely to fail observation when compared to small hemothoraces [OR 13.36, 95% CI 3.29-54.3, $p<0.001$].

More than half of moderate-sized hemothoraces may be observed safely without need for TT. Further research is needed to define an optimal cutoff point for placement of TT as well as to determine which additional factors contribute to successful observation. One limitation of this retrospective study is that the objective parameters guiding each physician’s decision of how to manage hemothoraces was limited. Thus, it was difficult to know whether TT was warranted in each case.
Postoperative Pain Management among Dominican and American Health Care Providers: A Qualitative Analysis

Christopher A. Devine, MPhil
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018
Rheumatology Research Foundation Medical Student Preceptorship

Jeffrey N. Katz, MD, MSc
Orthopedic and Arthritis Center for Outcomes Research
Brigham & Women’s Hospital, Harvard Medical School

US practitioners have prescribed increasing amounts of opioid analgesics in recent years, contributing to what the Centers for Disease Control (CDC) has declared as an opioid epidemic. Opioids are used frequently in the preoperative and postoperative periods for patients undergoing total joint replacement (TJR) in the US and other developed countries, but cross-cultural comparisons of this practice are limited. International medical missions such as Operation Walk Boston (OpWalk), a humanitarian program that provides TJR surgeries to financially vulnerable patients in the Dominican Republic (DR), offer a unique opportunity to compare postoperative pain management approaches in a developed and developing nation.

We interviewed American and Dominican surgeons and nurses (n = 22 total) during OpWalk 2015. We used a moderator’s guide with open-ended questions to inquire about approaches to postoperative pain management, opioid-sparing analgesia following TJR, and factors influencing prescribing practices. Interviews were conducted one-on-one in quiet rooms in the preferred language of the participant, lasted approximately 15 minutes, and were recorded digitally. Spanish interviews were transcribed verbatim into Spanish and translated into English by a translation company, and English interviews were transcribed by study investigators. Interview transcripts were analyzed using content analysis by two investigators.

Providers highlighted differences in the patient-provider relationship, pain medication prescribing variability, and access to medications. Dominican surgeons emphasized their adherence to standardized pain protocols and employed a paternalistic model of care, while their American counterparts reported prescribing variability and described shared decision-making with patients. Dominican providers described limited availability of potent opioid preparations in the DR, in contrast to Americans who discussed opioid accessibility in the US.

Several limitations of our study should be noted. American interviewees were primarily limited to Boston practitioners, and Dominican providers were all staff members of a single hospital. Thus, we cannot generalize to the entire US and DR. Our qualitative methodology also precludes claims of causality, so results are illustrative rather than definitive.

Our findings suggest that cross-cultural comparisons provide useful insight into how opioid prescribing practices, approaches to the patient-provider relationship, and medication access inform distinct pain management strategies in American and Dominican surgical settings. Moreover, our data indicate that incorporating cultural norms into pain management decision-making has the potential to yield similar or better outcomes with less reliance on opioid analgesics. This hypothesis may have important implications for patients undergoing painful surgeries in both the US and abroad, and merits formal testing.
Population-Level Evidence for an Association between Pulmonary Hypertension and Diabetes

Ryan S. Din
Harvard Medical School, Walter B. Cannon Society, Class of 2018

Kenneth Mandl, MD, MPH
Computational Health Informatics Program
Boston Children's Hospital

Pulmonary hypertension (PH) is a debilitating condition that is often preceded by other diseases such as heart failure, connective tissue disease, and HIV, in addition to having heritable and idiopathic etiologies. The pathophysiology of PH remains poorly understood and current treatment options are limited. Few studies have suggested a potential link between PH and diabetes, but the nature of this relationship remains poorly explored in the literature. Analysis of population-level data on PH may validate this association and provide novel insight into its mechanisms to help guide future therapies.

Claims data obtained from a large US employer-provided health insurance company were utilized for patients enrolled in 2006 (N=4,263,185). Diagnosis of PH was made by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes of 416.0, 416.8, and 416.9 occurring on three different dates in the same year, while diagnosis of type II or unclassified diabetes mellitus was similarly defined using the ICD-9-CM code 250.0. Congestive heart failure, coronary artery disease, and tobacco use disorder, common comorbidities of diabetes, were controlled for in our analysis and defined by the ICD-9-CM codes 428.0, 414.9, and 305.1 respectively. Children under the age of 18 were excluded.

1,751 adult patients with PH were identified: 1,162 females (66.4%) and 589 males (33.6%). The average age of PH patients was 70.9 ± 14.5. 458 PH patients (26.2%) had a diagnosis of diabetes mellitus, compared to 274,145 (3.7%) of patients without PH. The average age of patients with diabetes was 52.9 ± 21.5 years. Multivariate regression analysis controlling for patients with congestive heart failure, coronary artery disease, and tobacco use disorder, as well as age and gender, revealed that PH is a significant predictor for diabetes (p<0.001, Odds Ratio = 2.2, 95% Confidence Interval = 2.0-2.5, Table 1). Additional testing revealed that diabetes was a significant predictor of PH in our population when controlling for the same factors (Odds Ratio = 2.2, 95% Confidence Interval = 1.9-2.4, p<0.001, Table 2). Excluding patients with comorbid CHF, CAD, and smoking revealed an increased risk of diabetes given PH (Odds Ratio = 4.7, 95% Confidence Interval = 3.9-5.8, p<0.001, Table 3) as well as an increased risk of PH given diabetes (Odds Ratio = 4.8, 95% Confidence Interval = 4.0-5.7, p<0.001, Table 4). Age and gender were significant predictors in all models (p<0.001).

Patients with pulmonary hypertension may have an increased risk of diabetes mellitus and vice versa. The association between diabetes and pulmonary hypertension needs to be further explored.
Discovering Circular RNAs in Dopamine Neurons of Human Brain: Implications for Parkinson’s Disease

Alyssa C. Ehrlich
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Clemens R. Scherzer, MD
Ann Romney Center for Neurologic Diseases, Department of Neurology
Brigham and Women’s Hospital

To understand how the human brain functions in health and disease, a complete picture of genomic function in specific brain cells is needed. While considerable progress has been made on linear RNAs (such as messenger RNAs) transcribed in specific types of neurons, the world of non-linear, circular RNAs has been virtually unexplored in human brain. Here we show for the first time that hundreds of circular RNAs are robustly expressed in dopamine neurons of human brain, with potentially important implications for our understanding of diseases preferentially targeting this cell type, such as Parkinson’s disease.

Transcriptomes derived via deep sequencing of ribo-depleted RNA from substantia nigra dopamine neurons laser-captured from 65 postmortem human brains of patients with symptomatic Parkinson’s disease or subclinical disease, and healthy controls were analyzed. Transcriptomes were also acquired for pyramidal neurons and non-neuronal cell types. The CIRI algorithm was used to identify circular RNA candidates from transcriptome data. Counts of circular RNA reads were normalized to the total number of non-mitochondrial, non-ribosomal RNA reads. In total, 3,196 distinct non-ribosomal circular RNA candidates were identified, with at least two circular RNA reads in at least two healthy control samples. Of these candidates, 673 (21.1%) were uniquely expressed in dopamine neurons. Among the 1,847 circular RNAs identified in neurons of human brain, 528 (28.6%) had not been previously identified in human brain tissues. Expression of a highly abundant circular RNA, ciRS-7, was significantly higher in symptomatic Parkinson’s disease (14.61 reads per million, \( P < 0.001 \), Wilcoxon rank-sum test) than in age-matched healthy controls (7.06 reads per million). A link between Parkinson’s disease and ciRS-7 is supported by previous mechanistic data, which shows that ciRS-7 acts as a sponge (negative regulator) of miR-7, a microRNA that represses alpha-synuclein expression in cultured cells.

These emerging data hint at a major role for circular RNAs in human dopamine neuron biology and Parkinson’s disease. Additional experiments are needed to validate the novel circular RNA candidates here identified, as well as to further investigate potential mechanistic relationships between circular RNAs and Parkinson’s-related neuropathology.
Temporal Trends and Comparative Effectiveness of Bivalirudin versus Unfractionated Heparin for Percutaneous Coronary Intervention among Patients with Acute Myocardial Infarction: A Report From the National Cardiovascular Data Registry

Enrico G. Ferro
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018
American Heart Association Student Scholarship in Cardiovascular Disease

Robert W. Yeh, MD, MSc, MBA
Interventional Cardiology Associates, Department of Medicine
Massachusetts General Hospital

Background: Bivalirudin and unfractioned heparin (UFH) are the two most commonly used anticoagulants during percutaneous coronary interventions (PCI). Randomized trials have shown that bivalirudin, a direct thrombin inhibitor, reduces post-procedure bleeding rates compared with UFH, but may increase the risk of early ischemic events in patients with acute myocardial infarction (AMI). However, trials comparing bivalirudin to UFH may have been confounded by the differential use of glycoprotein IIb/IIIa inhibitors (GPI), an adjunctive anticoagulant used more commonly with UFH and independently associated with increased periprocedural bleeding. Further investigation into the absolute benefit of bivalirudin as compared with UFH in PCI for AMI is needed.

Objective: To describe the temporal trend in bivalirudin use during PCI for AMI in a nationally representative physician operator population, and to use an instrumental variable analysis to remove unmeasured confounding and compare the effectiveness of bivalirudin versus UFH.

Design, Setting and Patients: Analysis of data from 1,066,384 PCIs performed by 7,798 operators participating in the National Cardiovascular Data Registry CathPCI registry from July 1, 2009 through December 31, 2014. The proportion of bivalirudin use among operators was chosen as the instrumental variable to identify “high bivalirudin” operators who used bivalirudin in ≥75% of PCIs, and “low bivalirudin” operators who used bivalirudin in ≤25% of PCIs. Bivalirudin was compared to UFH by conducting unadjusted and adjusted instrumental variable analyses with the two-stage least squares methodology.

Main Outcome Measures: In-hospital bleeding and in-hospital mortality (NCDR Version 4 definition).

Results: Bivalirudin use increased linearly from 2009 through 2013, followed by a decline starting in 2014. There was a corresponding decrease in UFH with GPI use throughout this period, but an increase in UFH monotherapy starting in 2014. Preference for bivalirudin varied widely among operators. Bivalirudin was associated with a 3.05% absolute reduction in in-hospital bleeding (p<0.001), but no significant reduction in in-hospital mortality. In exploratory analyses, bivalirudin was associated with a 0.28% increase in in-hospital definite stent thrombosis (p<0.001). After instrumental variable analysis and additional adjustment for GPI use, the bleeding reduction and increase in stent thrombosis were attenuated but remained statistically significant.

Conclusions: Overall bivalirudin use increased throughout the study period, although a decline was observed starting in 2014. In the largest real-world population examined to date, bivalirudin was associated with a reduction in in-hospital bleeding and a marginal increase in in-hospital definite stent thrombosis. The higher rate of GPI use with UFH was only partly responsible for bivalirudin’s lower bleeding rate.
Simultaneous Mutation Detection and RNA-Seq in Single Cancer Cells

Jonathan M. Fisher
Harvard Medical School, Irving M. London Society, Class of 2018

Aviv Regev, PhD
Regev Laboratory, Klarman Cell Observatory
Broad Institute

Both genetic and epigenetic heterogeneity among tumor cells define cancer biology and pose a major therapeutic challenge, yet technical limitations have hampered our ability to dissect their interaction. Single-cell RNA-seq yields powerful information about the variation of gene expression between cells in a population, but corresponding genetic differences between cells are largely invisible.

Here, I present a new strategy to capture genetic and epigenetic information simultaneously from single cancer cells. Single-cell RNA-seq via the SMART-seq2 method produces PCR-amplified transcripts from single cells, and many key oncogenic mutations are expressed at the RNA transcript level. However, due to the dynamic range of gene expression, whole-transcriptome libraries from single cells tend to bear low complexity wherein a few highly-expressed transcripts dominate the sequencing space. Therefore, with the help of others in the lab, I developed a method to selectively amplify and detect mutations from mRNA transcripts using quantitative PCR with primers specially designed to specifically anneal to mutant versus wild-type cDNA sequence.

Specifically, we tested our transcript mutation-calling qPCR method on two oligodendroglioma cell lines, BT54 and BT88. From prior single-cell RNA-seq, we inferred two mutations specific to BT54 and three mutations specific to BT88. We designed mutant- and wild-type-specific qPCR primers for each mutation and verified primer viability using artificial templates mimicking transcript targets. Next, we assayed mutation status by performing qPCR on bulk samples of BT54 and BT88. Four of the five mutations were present as expected, and one mutation was absent, suggesting a false positive mutation call from prior single-cell RNA-seq. We then tested the primers in 40 single cells each from BT54 and BT88 cell lines. Approximately 15 cells from each cell line showed no amplification with any qPCR primer set, suggesting whole cell loss upstream of transcriptome processing. Among viable single cell transcriptomes, approximately 90% of single cells demonstrated specific amplification from wild-type- or mutant-specific primers.

We conclude that our qPCR mutation calling approach can accurately and specifically detect mutations on transcripts from single cells. Our method is optimized to work in concert with SMART-seq2 single-cell RNA-seq, allowing RNA sequencing and mutation detection qPCR from the same cell. This has profound application to study the interaction between genomic and epigenomic heterogeneity within a tumor.
Quality of End-of-Life Care for the Myelodysplastic Syndromes: Findings from a Large National Database

Sean Fletcher
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

Gregory A. Abel, MD, MPH
Division of Population Sciences, Department of Hematologic Oncology
Dana-Farber Cancer Institute

End-of-life (EOL) care has been shown to be more intensive for blood cancers compared to solid tumors; however, data are sparse regarding predictors of intensive care unit (ICU) use in the last 30 days of life and hospice enrollment among patients with specific hematologic malignancies. Moreover, little is known about EOL care specifically for the myelodysplastic syndromes (MDS), which are distinguished among the blood cancers by their relative indolence in many patients and high rate of transfusion dependence.

We conducted a retrospective analysis using the Surveillance Epidemiology and End Results (SEER)-Medicare database. Patients ≥ 65 years of age who had a primary diagnosis of MDS between 2006 and 2011, lived for at least 30 days after their diagnosis, and died prior to December 31, 2012 were eligible for inclusion. Outcomes were two well-established quality measures for EOL care in oncology: ICU admission within the last 30 days of life (an indicator of poor quality), and enrollment in hospice for any length of time (an indicator of good quality). After determining their overall prevalence, we fit multivariable logistic regression models to investigate sociodemographic and clinical associations with each outcome.

A total of 6,955 MDS patients were eligible. Overall, 28% were admitted to the ICU in the last month of life, and 49% had enrolled in hospice. In multivariable analyses, transfusion-dependent patients were more likely to be admitted to the ICU and less likely to enroll in hospice (both p<0.001). Nonwhite patients were less likely to enroll in hospice and more likely to be admitted to the ICU at the end of life (both p<0.001). Patients who died in later years had a higher prevalence of ICU admissions (p=0.05) and were more likely to enroll in hospice (p=0.001).

Only about half of the MDS patients in our cohort were enrolled in hospice; however, the odds of enrollment increased over time. Interestingly, the odds of ICU admission within the last 30 days of life also increased over time, a trend that has been seen in solid tumors. As bone marrow failure in MDS can lead to reversible sepsis and the need for temporary blood pressure support, it is difficult to determine if this trend truly represents a worsening in quality of EOL care. Finally, our finding that transfusion-dependent MDS patients were less likely to receive hospice suggests that one reason for suboptimal enrollment is that the current hospice model—which largely disallows transfusions—is not meeting the specific palliative needs of this population.
When do women decide to undergo sterilization? A qualitative study to evaluate the utility of the federally-mandated Medicaid waiting period

Olivia Foley
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Caryn Dutton, MD
Brigham and Women's Hospital
Department of Obstetrics and Gynecology

Female sterilization is the most prevalent contraceptive method reported among married women and the second most commonly used birth control method for all women of reproductive age in the United States. Since 1979 the federal government has required a waiting period of at least 30 days between written consent and a sterilization procedure for Medicaid patients. Private insurance patients have no such required waiting period. Though designed to protect the reproductive rights of vulnerable populations, the Medicaid sterilization consent form (SCF) and associated waiting period appear to limit access to one of the most popular methods of contraception on the basis of socioeconomic status. Given this disparity, it is crucial to understand whether the mandated waiting period adds value to the decision-making process for women considering sterilization. Therefore, this qualitative study aims to:

I. Describe the perceived value of a 30-day waiting period for women’s decision-making regarding postpartum sterilization, comparing responses among women who did and women who did not sign the SCF 30 days prior to undergoing sterilization.

II. Assess the time frame during which women who undergo postpartum sterilization consider this option and finalize their decision.

III. Explore why the mandated waiting period might add value to the decision-making process relative to personal characteristics and beliefs.

To address these goals our study is enrolling women at Brigham and Women’s Hospital (BWH) who have undergone postpartum sterilization (PPS). These women are consented to participate in a 20-minute interview regarding their decision-making process surrounding PPS. All interviews are recorded and transcribed. To date, eighteen of our planned twenty-five participants have been recruited.

After completing enrollment, we will use grounded theory methods to code and generate themes identified in the transcribed interview responses. ATLAS.ti 7.0, a qualitative research software program, will be utilized to organize and compare coded transcripts. Major themes and patterns observed and relevant to our study goals will be described and illustrated through representative quotations.

Because we are recruiting participants who have undergone postpartum sterilization, we are not including women who requested information about the procedure, those who had planned on undergoing PPS but decided on another option, and those experiencing medical or logistical barriers to fulfillment of a sterilization request. Our conclusions can be generalized only to women who receive sterilization but will add needed context to the discussion regarding access to contraception and reproductive health for women dependent on Medicaid.
Heart Failure Outcomes in Stable Patients with Prior Atherothrombosis: Observations from the TRA 2°P-TIMI 50 Trial

Benjamin L. Freedman
Harvard Medical School, Francis Weld Peabody Society, Class of 2018

David A. Morrow, MD, MPH
TIMI Study Group, Cardiovascular Division, Department of Medicine
Brigham and Women's Hospital

Heart failure (HF) affects 5.7 million Americans presently, and engenders substantial morbidity and mortality. Because coronary artery disease is now the largest contributor to HF, it is important to evaluate the impact of antithrombotic therapies on the incidence and severity of HF in randomized clinical trials. To this end, we aim to develop an analysis approach to determine HF incidence in a clinical trial where HF was not captured a priori as a clinical endpoint. We are developing such an approach to determine the incidence of new/worsening HF among participants in the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2°P)-TIMI 50 trial, which examined cardiovascular outcomes in 26,449 stable patients with atherothrombosis randomized to placebo or vorapaxar (a novel antiplatelet agent) on top of standard therapy. To ascertain HF events in this trial, we developed a definition of HF based upon objective clinical criteria and are using it to adjudicate HF events among 1,960 serious adverse events (SAEs).

From a total of 10,962 SAEs reported in the TRA 2°P-TIMI 50 trial, we identified 1,960 potential HF events based on their event terms. To qualify as a “definite HF” event, an SAE had to meet the HF endpoint criteria proposed by cardiovascular professional societies (Hicks et al., JACC 2015). For sensitivity analyses, we developed and implemented a tiered HF definition comprising four mutually exclusive categories: “definite HF,” “probable HF,” “possible HF,” and “HF not excluded.” Ultimately, all 1,960 SAEs will be adjudicated in parallel by two investigators; discrepancies will be resolved by group consensus.

Of the 940 SAEs adjudicated to date, 20% qualify as “definite HF,” 35% as “probable HF,” 30% as “possible HF,” 7% as “HF not excluded,” and 8% as “HF excluded.” After adjudicating all potential events, we will pursue the following additional aims: (1) to determine the incidence of new or worsening HF among participants in the TRA 2°P-TIMI 50 trial; (2) to identify clinical risk factors for HF; and (3) to assess whether vorapaxar modifies the risk of developing new or worsening HF in this population.

Based on our preliminary data, structured review of SAE appears to be a feasible method for determining HF incidence post hoc in clinical trials. The major challenge we have encountered is preserving the sensitivity and specificity of our analysis as we develop a definition of HF to adjudicate SAEs with significant variability in the clinical detail reported.
Piezo2 is a mechanosensitive ion channel that functions by adapting mechanically activated currents and by mediating tactile transduction. Mutations in human Piezo2 proteins have been associated with a variety of disorders and several syndromes have craniofacial anomalies and muscle contractures as prominent features. One such disorder is Gordon syndrome (OMIM-#114300), which is characterized by debilitating congenital contractures and occasionally an incompletely penetrant cleft palate.

To better understand the function of Piezo2 in vertebrates, we identified 4 different zebrafish Piezo homologs. To molecularly characterize zPiezo2 homologs, whole mount in situ hybridization was performed in wild type fish. Expression was noted in the pharyngeal arch epithelium, sensory neurons of the CNS and myocytes throughout the tail. We analyzed the function of zPiezo homologs using antisense morpholino oligonucleotides (MOs) and a zPiezo2 mutant was also developed. To identify craniofacial defects in zPiezo, we compared the pattern of cartilage in zPiezo morphants and mutant larvae with wild-type using Alcian blue staining. Larvae injected with MOs to one homolog, zPiezo2a.2, show significantly reduced or absent branchial arch cartilages. However, mutant zPiezo2b larvae did not display a craniofacial phenotype, potentially due to maternal inheritance or redundancy between the different zPiezo homologs in zebrafish. Characterization of a muscle phenotype in mutant zPiezo2 fish through electron microscopy of the tail revealed a mitochondrial defect in the myocytes. These results suggest that Piezo2a.2 is specifically required for normal pharyngeal cartilage formation in zebrafish and the muscle abnormality phenotype seen in zPiezo2b mutants may be due to a development defect in mitochondria. Identifying where Piezo2 is expressed and its loss of function phenotypes will help elucidate its role in muscle and craniofacial development.
The Effect of Point-of-Care Price Information on Outpatient Pediatric Physician Ordering Behavior

Smitha Ganeshan
Harvard Medical School, Oliver W. Holmes Society, Class of 2018

Alyna Chien, MD, MS
Department of General Pediatrics
Boston Children's Hospital

Prior price transparency research has not focused on pediatric physicians. Primary care physicians (PCPs) and specialists may differentially ignore, lower, or raise ordering rates depending on whether prices are perceived as higher or lower than anticipated. We studied the effect of providing two different forms of price information to pediatric PCPs and specialists for pediatric outpatient procedures (e.g., CTs, sleep studies).

The primary population studied included 791 primary care and 505 specialist physicians practicing in a large multi-specialty group in Massachusetts. In January 2014, we block randomized 1,296 pediatric physicians to 3 study arms. Physicians in control Arm 1 received the median amount paid per procedure via a written memo once at the beginning of the year; physicians in intervention Arms 2 and 3 additionally received price information through their electronic health record (EHR) whenever placing orders throughout 2014. Arm 2 physicians were given one median price; physicians in Arm 3 were provided paired “inside” and “outside” prices. All prices were based on paid claims and not charges. Using logistic regression, we calculated the per encounter odds of an order being placed in the intervention arms relative to the control arm before (2013) and after the intervention (2014) years, clustering on physicians. We fit separate models for PCPs and specialists.

The adjusted odds of an order being placed by physicians in the control Arm 1 was not significantly different during the intervention year compared to baseline for both PCPs and specialists. EHR-based point-of-care single median price information was associated with significant increases in the odds of an order being placed for both PCPs and specialists (AOR Arm 2 vs 1: 1.11 [1.05, 1.18] and 1.23 [1.06, 1.44], respectively). In contrast, paired “inside” and “outside” median price information was associated with significantly greater odds of an order being placed among PCPs (AOR Arm 3 vs 1: 1.10 [1.03, 1.17]), but significantly lower odds among specialists (AOR Arm 3 vs 1: 0.86 [0.74, 0.99]).

Based on this data, we conclude that providing outpatient procedure price information to pediatric physicians can have a neutral, lowering or heightening effect depending on the type of price information and physician type.

The major limitation for the pediatric analysis was in defining a pediatric provider. For the purposes of this analysis, a pediatric provider is defined as any clinician who had at least one visit with a child under the age of eighteen in 2013 and 2014.
Analysis of outcomes, complications, and direct costs in patient undergoing lobectomy for stage I lung cancer

Abraham Geller
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Douglas Mathisen, MD
Hermes C Grillo Professor of Thoracic Surgery
Division of Thoracic Surgery, Department of Surgery
Massachusetts General Hospital

Lobectomy is the current standard of care for stage I non-small cell lung cancer (NSCLC), among the most common cancers diagnosed in the United States. Despite this, little quantitative information exists regarding the rates and costs of complications of lobectomy. Efforts to improve patient outcomes following lobectomy while containing costs would benefit from understanding the rates of various postoperative complications, as well as their respective costs.

We hypothesize that complications may represent a significant fraction of the cost of care for lobectomy patients. We aim to quantify the fractional cost of complications in lobectomy patients (i.e. the proportion of total cost attributable to complications alone). Our primary endpoint is the overall difference in cost of care for patients with postoperative complications compared to patients without. Secondary endpoints look at the fractional cost of each adverse event considered. Our goal is to identify specific high-cost complications as “leverage points” whose reduction may significantly curb costs.

To test this, we conducted a retrospective study of patients at the MGH. The Research Patient Data Registry (RPDR) is the centralized clinical data warehouse of the MGH. The RPDR was queried for patients who underwent lobectomy for stage I NSCLC between 2009 and 2014. Exclusion criteria were applied to ensure data quality. Complications and cost of encounter were recorded for each patient, and patients were stratified by complications. Total encounter costs were then compared between patients suffering complications and those with an uncomplicated postoperative course in order to determine the costs attributable to complications alone.

The total cost of care (surgical and postoperative) was significantly greater among patients suffering any postoperative complications compared to patients without complications (156% increase, P < 0.0001). Cost increased by an average of 168% in patients experiencing at least 1 major complication compared to patients without complications (P = 0.001). In general, the fractional cost of care increased by 155% for patients experiencing one major postoperative event, and by 290% for patients experiencing two or more events (P = 0.16).

Preliminary results indicate that adverse postoperative events, especially major events, contribute significantly to overall cost of care for lobectomy patients. Our ongoing work seeks to improve statistical significance and allow us to stratify our analysis according to specific complications of interest. Based on this work, it may be possible to reduce the cost of care for lobectomy patients by 30-65% simply by improved postoperative care and eliminating major complications.
Involving “Persons with Patient Experiences” in Healthcare Quality Improvement and Redesign: Lessons from Region Jönköping County, Sweden

Galina Ghehman
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

Mr. Goran Henriks
Chief Executive of Learning and Innovation, Qulturum
Region Jönköping County, Sweden

How do we know if a change is an improvement? Involving citizens and patients in healthcare quality improvement is increasingly being recognized as a key strategy for making changes that matter to patients and achieving the Triple Aim—improved outcomes, lowered costs, and improved experience. While relatively new in the US, in Sweden a focus on strengthening patient engagement has been a stated policy aim for over three decades. As a result, Sweden’s health system has developed unique approaches to partnering with “individuals with patient experiences” and may offer lessons for how to effectively engage patients in quality improvement and redesign.

The purpose of this project was to: (1) explore how patient involvement is defined, conceptualized, and implemented in Region Jönköping County, Sweden; (2) identify the barriers and facilitators to involving patients; and (3) highlight the value of involving patients in improvement work, as well as best practices for doing so.

Twenty-three semi-structured interviews, as well as site-visits and in-person observations at two of the county’s three hospitals were conducted. Participants included healthcare providers, administrators, and managers, improvement coaches, political leaders, and persons with patient experiences. Key themes, findings, and strategies were identified using grounded theory qualitative analysis.

Findings: patient involvement takes various forms and occurs at multiple levels within the healthcare system. In Jönköping, such involvement began twenty years ago with the introduction of “microsystem thinking” and has since evolved. Challenges to involvement are psychological and cultural barriers (providers believing they know what’s best, being hesitant to share mistakes, or resisting ceding control to patients while taking on a “coaching role”) and logistical barriers (time, resources, recruitment). Key provider-, patient-, and system-based facilitators include open-minded and humble professionals, effective patient partners, and leadership support for a culture of improvement, respectively. Benefits to involvement are selecting more relevant improvement projects, understanding patients’ experiences, and proposing innovative solutions.

Patient partners make a significant contribution to quality improvement, by focusing efforts on what matters most and offering expertise on the experience of care. Moreover, meaningful engagement increases patients’ knowledge and self-management. While health providers’ attitudes remain an important barrier, committed leadership can promote a system and culture of continuous improvement where patient input is sought and valued. The impact of patient involvement was not quantitatively assessed, but several successful examples and their outcomes were identified. This project offers lessons on why patients should be engaged, and guidance for how to do so.
Improving the Versatility of Genome Editing: Screening and Characterizing Cas9 Orthologues

Jingyi Gong
Harvard Medical School, Irving M. London Society, Class of 2018

J. Keith Joung MD, PhD
Molecular Pathology Unit, Department of Pathology
Massachusetts General Hospital

The CRISPR-Cas9 platform enables targeting of specific genetic loci and alteration in the expression level of specific genes. The system consists of two main components: a guide RNA and the Cas9 protein. Guide RNAs are short RNAs that can be engineered to target a specific genomic sequence when complexed with Cas9. Cas9 is a multi-function protein that includes two putative nuclease domains. Although the guide RNA/Cas9 complex is primarily directed to its target by complementarity of the variable part of the guide RNA with the genomic DNA site, Cas9 must also recognize a short adjacent sequence known as the protospacer adjacent motif (PAM). Therefore, the range of sequences that can be targeted is limited by the requirement of this PAM. One way to improve the targeting range of the CRISPR-Cas9 system is via discovery and characterization of new Cas9 orthologues. The goal of this project is to assemble and characterize additional Cas9 orthologues that possess potentially different PAM specificities and to test their activities in human cells. Furthermore, the orthologues may also impart other advantageous properties such as smaller size, or improved genome-wide specificity.

There are over 600 predicted Cas9 orthologues in publicly available databases. The therapeutic potential of the platform is limited by the capacity of delivery virus. Cas9 proteins of smaller size and with predictive PAM information were prioritized for characterization. We assembled human codon optimized blocks of DNA encoding parts of these Cas9 proteins using the Gibson assembly method. I plan to characterize the activities of these Cas9 orthologues and their associated guide RNA sequences using two different methods previously developed by the Joung lab: (1) a bacterial cell-based system in which site-specific cleavage of a toxic plasmid by a guide RNA/Cas9 enables cell survival; and (2) a human cell-based assay in which site-specific cleavage of a constitutively expressed GFP reporter leads to loss of cell fluorescence, which can be quantified by flow cytometry.

Continuing the work by a previous lab member, I have assembled two Cas9 proteins and designed guide RNAs to target sites in the bacterial toxic plasmid and also in the GFP reporter gene. I have begun testing these Cas9 proteins in the bacterial system and am currently optimizing conditions for this assay. In the next step, I plan to examine the activities of these gRNA/Cas9 orthologues in our human cell-based EGFP disruption assay. The successful characterization of Cas9 orthologues with novel PAM specificities and smaller sizes will both expand the targeting range of this important platform and improve prospects for therapeutic applications.
Modeling Hypnotic Overuse in Insomniacs

Frank Gonzalez
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Matt Bianchi, MD, PhD
Division of Sleep Medicine, Department of Neurology
Massachusetts General Hospital

Insomnia is a sleep disorder that is generally characterized by a complaint of difficulty falling or staying asleep, as well as daytime symptoms including sleepiness. Estimations on the prevalence of insomnia in the US ranges from 1% to 33% with individuals suffering a significantly decreased quality of life as well as medical consequences including cardiac disease.

Current treatment is focused on pharmacological therapy with little evidence to support its efficacy and cognitive behavioral therapy has emerged as a suitable alternative for certain subsets of insomniacs, particularly those in which sleep misperception and night-to-night variability is a concern. In those individuals, we hypothesize that there is a proportion of insomniacs that are misattributing the body’s natural homeostatic rebound to a hypnotic.

With these thoughts in mind, we set out to generate a model that captures the stochastic, night-to-night variability in objective total sleep time and role of homeostatic pressure, which are two key features of chronic insomnia. Furthermore, by taking a combination of clinically relevant parameters, we aim to quantify the misattribution of increased total sleep time to hypnotics as opposed to the body’s homeostat while also determining the length of time needed to observe such individuals before being able to conclude that they are indeed having misperception.

In order to generate the model, MATLAB was used as the script platform. Objective total sleep time, subjective total sleep time, and hypnotic use were the main parameters observed and were influenced by physiological arousal, rumination, reactivity to a poor night’s sleep, probability of addiction, and the body’s homeostat. Weight given to each factor were taken from recent literature on the topic. In the script, the current night’s sleep was influenced by the prior night’s sleep by using a probabilistic function that included Gaussian variability.

The current model script generates probabilistic simulations of objective total sleep time, subjective total sleep time, and number of nights on which a hypnotic was taken for a year’s time. Analysis is ongoing and includes quantification of mismatch between objective and subjective total sleep time and the minimum length of time an individual’s sleep patterns must be observed before sleep misperception phenotype is identified.

While the model is only theoretical, we are hopeful that it can guide future projects using wearable sleep monitors to discover individual insomnia phenotypes since current sleep testing is only short term in duration and not often conducted for insomnia management.
Retrospective Analysis of Arthroscopic Surgery (lysis and lavage): Relationship between Clinical Presentation, Comorbidities, and Outcomes.

Gabriel Grisham
Harvard School of Dental Medicine, Cannon Society, Class of 2018

Steven J. Scrivani, DDS, DMSC
Director, Division of Oral and Maxillofacial Pain
Department of Oral and Maxillofacial Surgery, Massachusetts General Hospital

Arthroscopic lysis and lavage (ALL) is an important treatment option for disorders of the temporomandibular joint (TMJ). Prior studies show that for certain conditions, ALL is just as effective as more invasive operative procedures. With success rates reported between 65-80%, outcomes could be improved further by more effectively identifying good candidates for the procedure. To this end, this study will analyze the relationship between clinical presentation, specific comorbidities, and outcomes for ALL.

We hypothesize that:

1. Initial ALL is a successful procedure based upon specific criteria.
2. There will be a set of clinical factors and specific comorbidities that correlate with ALL success or failure.
3. In those patients that had prior surgical procedures, there will be a set of clinical factors and specific comorbidities that warranted the need for another ALL.
4. In those patients that went on to have a second ALL or joint arthroplasty, there were a set of clinical factors and specific comorbidities that correlate with initial ALL failure.

From September 2010 through April 2015, over 250 ALL procedures were performed by Dr. David A. Keith at Massachusetts General Hospital. This retrospective cohort will be used to:

1. Determine the success rate of ALL.
2. Evaluate specific clinical factors and patient comorbidities and correlate these with ALL success or failure.
3. Isolate patients with prior surgery, and determine if they have differences in success when compared to those without prior surgery.
4. Isolate patients who progressed to arthroplasty and evaluate specific clinical factors and patient comorbidities and correlate these with success or failure compared to ALL.

All data will be collected from patient electronic medical records. A database will be created using Microsoft Excel 2013 with appropriate checks to identify errors. Descriptive statistics will be computed for all of the study variables. A univariate regression model will be developed to identify those variables and predictors that will be associated with the outcome variables. Variables or predictors with p-values ≤ 0.15 on the univariate analysis together with biologically relevant factors, age, and gender will be entered into a multivariate linear mixed-effects regression model if the outcome of interest is continuous, or the multivariate logistic regression model if the outcome is binary. The analytic method will adjust for clustering outcome observations within the same patient. The SAS Statistical Software Computing Environment Version 9.3 will be used.

Results for this study have not yet been determined.
Correlating Gait Variability after Increased Cognitive Load with Brain Volume and Cortico-spinal Myelin Content in Cognitively intact Parkinson’s disease Patients: A Pilot Study

Ricardo Guerra
Harvard Medical School, Francis Weld Peabody Society, Class of 2018
Bertarelli Summer Research Fellowship

Bogdan Draganski, MD
Laboratoire de Recherche en Neuroimagerie (LREN)
Centre Hospitalier Universitaire Vaudois (CHUV)

Gait difficulty remains a hallmark of Parkinson’s disease (PD), a neurodegenerative disorder affecting about 1% of people over age 60, but objectively measuring gait remains a challenge in clinical and research settings. Recently, motion sensor accelerometers have shown to calculate accurate and precise gait outcome measures.

PD patients demonstrate decreased stride speed while walking a straight path compared to healthy controls. Detecting these changes in cognitively intact PD (PD-CI) patients can be difficult and provides controversial results. Gait problems usually precede cognitive deficits, so dual task paradigms are utilized to prevent cognitive compensatory mechanisms from masking underlying motor-related pathology.

Gray matter cortical atrophy appears in PD patients with mild cognitive decline, but it remains to be seen if such changes can be demonstrated in PD-CI patients and whether these changes correlate with gait difficulty. The purpose of this study is thus two-fold: (1) to validate spatio-temporal gait analysis equipment as a sensitive, noninvasive tool by examining gait changes in PD and healthy control subjects during a dual task walking paradigm and (2) to investigate the relationship between gait performance and structural brain data analysed in the framework of voxel-based morphometry.

We hypothesized worse gait performance in PD-CI patients when walking a straight 20m path, with exacerbated effects performing a dual task (counting backwards and holding a water-filled glass) simultaneously. In our subjects (n=17), results demonstrated significantly reduced speed in PD-CI patients in baseline (p=0.021) and dual task condition (p=0.040). Differences in other gait parameters were not significant, but directionality was consistent with our predictions.

Our subjects’ structural MRI images indicated a positive correlation between bilateral cerebellar gray matter volume (GMV) and baseline speed (p<0.001). There was a stronger, positive correlation between baseline speed and GMV near the motor cortex in PD-CI than in control subjects (p<0.05), perhaps a compensatory effect necessitating hyperactivity. Myelin content, which improves sensory integration involved in gait, was correlated positively with baseline speed in the superior parietal lobe and right cerebellum, and there was a stronger, positive correlation between speed and myelin in bilateral putamen and cerebellum in PD than in control subjects(p<0.01). White matter myelin content demonstrated stronger, positive correlation at corticospinal and fronto-striatal tracts with baseline speed in PD-CI subjects (p<0.05).

Although a larger cohort minimizing confounders is required to validate these results with family-wise error corrections, our pilot study identifies trends between objective gait measures and structural correlates which can inform earlier detection and diagnosis of this debilitating disease.
Analysis of State Policies and their effects on Freestanding Emergency Departments

Catherine Gutierrez
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

Jeremiah Schuur, MD, MHS
Assistant Professor of Emergency Medicine
Brigham and Women's Hospital

Emergency departments have long played a critical role in the U.S. healthcare system. They have served as the portal for half of all hospital admissions, responsible for 11% of ambulatory visits and a quarter of acute care visits. Patients are drawn to emergency departments for nonemergency care as well, largely due to long wait times for appointments, limited after-hours care at physician offices, lack of health insurance and barriers to access.

Until recently, almost all EDs were physically part of hospitals. The concept of freestanding emergency departments (FSEDs) was introduced in the mid-1970’s, and the number of FEDs has grown dramatically since – swelling from 55 in 1978 to around 222 in 2009. FSEDs have gained increasing attention because of their potential to provide high-quality emergency care to medically underserved areas, as well as relieving the burden of nearby EDs. More recently, however, there has been concern voiced by popular press claiming that FSEDs add additional expense to the health care system and encourage use of emergency services for nonemergency complaints.

Given the rising presence of FSEDs in the U.S., it is important to understand their role in the U.S. health care system. In this study, we sought to determine if FSEDs are equivalent to hospital EDs in terms of services provided, and we considered the role of state government in regulating these health care facilities.

We utilized several sources for this study, including state Department of Health representatives and statutes available on their websites. We also utilized Westlaw, an online legal research service, to access policies not available online. Statutes identified through these methods were organized into categories that include licensing and operational requirements, such as license fees, population and distance requirements, transfer agreements, Certificate of Need and Emergency Medical Treatment and Labor Act (EMTALA) regulations.

To date, we have succeeded in collecting the majority of the data necessary to generate a descriptive analysis regarding the impact of state regulations on FSEDs, with the limitation that some policies were unavailable through our sources. Following a second revision of the data, we plan to categorize our findings to demonstrate whether individual states regulate licensing and operational characteristics differently, their participation in EMTALA and Certificate of Need programs, and ultimately how these policies may affect the number of FSEDs in each state. Our analysis will consist of potential implications and policy recommendations given growth trends in individual states and current FSED regulations.
Examining Loss to Follow-Up in an Outpatient Under-nutrition Treatment Program in Saint Nicholas Hospital (Haiti): Implications for Improvement

Anand Habib
Harvard Medical School, Peabody Society, Class of 2018

Michelle Morse MD, MPH
Clinical Instructor in Medicine
Department of Global Health and Social Medicine Affiliate
Deputy Medical Director (Zanmi Lasante)

While evidence exists that ready-to-use therapeutic foods (RUTF) are effective in combating acute malnutrition, Zanmi Lasante (ZL) has encountered problems with achieving target cure rates of over 75%. Between January and April 2015, of the 444 patients exiting the out-patient treatment program (OTP) at Saint Nicolas Hospital (Saint Marc), the largest participating OTP site, 49% were lost to follow up (LTFU). We have some hypotheses for why LTFU may be high, including (a) financial and transportation barriers to attending follow-up appointments, (b) RUTF supply chain issues, and (c) participant families’ misunderstanding of the RUTF regimen.

This study employs a mixture of ethnographic and semi-structured qualitative interviews to understand the causes for the significant LTFU among children enrolled in ZL’s under-nutrition OTP at Saint Nicholas Hospital. Of the children who were deemed cured after completing the RUTF regimen and of the children who were enrolled in spring 2015 but who abandoned treatment, purposive sampling was used to identify ten enrollees from each group (twenty in all). In semi-structured interviews between the investigators, community health workers and the children’s parents/guardians carried out over seven weeks in summer 2015, we discussed (a) their understanding of the causes of their children’s under-nutrition, (b) how they administered their child RUTF, (c) challenges they faced in adhering to the regimen, (d) social practices around food consumption, and (e) their overall impressions of the program. Transcribed interview data from both groups was analyzed separately to distill recurrent themes and then compared to evince potential reasons why some children, but not others, complete treatment.

Interview analysis reveals two salient findings. First, there was a general lack of understanding of why children became malnourished, what Nourimanba (the RUTF manufactured by ZL) is, and how children could avoid relapse into malnutrition. Second, the families of children who completed the treatment and those who failed to complete the regimen both reported cost of transportation as the most significant obstacle to participating in the OTP. Sacrificed wages, long waiting times, lack of supervision for other children, and supply chain issues were not endorsed as significant challenges to program participation. Those who completed the program seemed to have greater social support which enabled them to borrow money necessary to travel to the clinic. While having only surveyed 20 participants, this study hopes to inform efforts to improve ZL’s delivery of RUTF treatment throughout Haiti’s Lower Artibonite Valley.
Assessment of Provider Nonverbal Communication and the Patient-Doctor Relationship within Various Health Settings

Tyler Haeffs
Harvard School of Dental Medicine, Francis Weld Peabody Society, Class of 2018

Maria Dolores Navarro Rubio, MD, MSc, MPH, PhD
Albert J. Jovell Institute of Public Health and Patients
International University of Catalonia

Communication is a crucial component in developing a positive doctor-patient relationship. Specifically, nonverbal communication has been proven by several studies to play a central role in conveying emotional and relational information in various settings. The few studies of nonverbal communication in clinical interactions have rarely focused on natural settings with real clinicians and patients. In particular, primary health centers and hospitals are two natural settings of particular interest in regards to differences in health care delivery. An analysis of the differences in nonverbal communication between these settings could provide valuable insight to the extent to which nonverbal communication affects clinically relevant outcomes.

The patient-doctor relationship is a frequently used indicator for gauging the quality in health care as it affects clinical outcomes, medical malpractice claims, and patient retention. Previous studies have pointed out the potential link between nonverbal communication and patient-doctor relationships, but differ on the extent to which they are connected. In this study we assess the differences in provider nonverbal communication and the patient-doctor relationship as perceived by the patient within general medicine clinics and primary health centers throughout Barcelona, Spain. Because patients typically visit their primary care physician more frequently than a hospital physician, we hypothesized that on average, providers from primary care centers would score higher on an evaluation of nonverbal communication and the patient-doctor relationship as perceived by the patient.

To test this hypothesis, non-emergent medical encounters from primary health centers (n=42) and various hospital departments (n=123) were analyzed. For each consultation, provider nonverbal communication was scored using a verified CICAA scale, while patient-doctor was evaluated using a verified patient-doctor relationship scale (PDRQ-9). A two-tailed statistical test was then performed for the averages of the nonverbal communication and patient-doctor relationship surveys from both health settings. The data from this study suggests a significant difference (p=.0221) in nonverbal communication, with medical providers from primary health centers scoring better than those from various departments within hospitals. However, there was no significant difference (p=.4395) in the patient-doctor relationship as perceived by the patient.

These results indicate that primary health care providers may connect better nonverbally with their patients than do medical providers in the hospital setting. However, this improved connection alone is not enough to favorably skew the patient-doctor relationship as perceived by the patient. This suggests that more factors, such as verbal communication, are necessary in order to substantially improve the patient-doctor relationship.
Developing and evaluating a surgical iAE reporting tool to comprehensively assess surgical outcomes

Kelsey Han
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Haytham Kaafarani, MD MPH
Department of Surgery, Division of Trauma, Emergency Surgery, and Critical Care
Massachusetts General Hospital

Health outcomes research estimates that adverse events occur in 14% of patients receiving surgical care. Decreasing the incidence of surgical adverse events should be prioritized given the high volume of surgeries (approximately 51 million inpatient surgeries) performed on an annual basis in the United States. To date, primary quality assessment databases such as the National Surgical Quality Improvement Program, Institute for Healthcare Improvement, and Agency for Healthcare Research and Quality Inpatient Quality Indicators focus primarily on preoperative or postoperative adverse events. This is problematic for two crucial reasons: (1) these systems are not set up to collect and analyze intraoperative adverse event (iAE) data in particular and (2) they may not capture the actual occurrence of most iAEs, as many surgeons perceive barriers in outcomes reporting. Consequently, the area of intraoperative adverse events (iAEs) warrants further investigation compared to its counterpart indicators.

iAE reporting represents a crucial step in improving patient safety. A surgical iAE reporting tool is important not only for detecting iAEs which cause harm, but also in recognizing “near miss” iAEs that do not impact the well-being or morbidity of the patient but indicate underlying weakness of a process or system. The development of a surgical iAE reporting tool and the collection of comprehensive iAE data are significant because iAE data informs quality improvement processes, allows accurate detection of broken systems or factors contributing to iAEs, and addressing iAEs has financial ramifications on health delivery systems. This stage - detection and reporting of an iAE - is currently the missing link in the process and will be the focus of this research project. Specifically, this project will examine surgeon attitudes concerning iAE reporting, with a particular emphasis on the emotional toll and support systems for iAE reporting, barriers to iAE reporting, and surgeon preferences for implementing an institutional reporting system.

Surveys will be distributed in mid-September to surgeons at Massachusetts General Hospital, Brigham and Women’s Hospital, Beth Israel Deaconess Medical Center, and Boston Children’s Hospital and data will be analyzed accordingly. Results of this survey will drive the creation of an iAE reporting tool. An anticipated limitation is that it is unclear how transferable this iAE reporting tool will be at other institutions with different hospital cultures or attitudes towards iAE reporting.
The effect of osteocyte-specific deletion of Antxr1 on bone mineralization

Sung Hyon Han
Harvard School of Dental Medicine, William Bosworth Castle Society, Class of 2018

Tatiana Besschetnova
Department of Developmental Biology
Harvard School of Dental Medicine

GAPO syndrome is a rare autosomal recessive disorder characterized by Growth retardation, Alopecia, Pseudoanodontia, and Ocular manifestation. Recent genetic studies identified loss-of-function mutation of the gene for anthrax toxin receptor (Antx), also called Tem8, as the causal factor for the generalized defect in extracellular-matrix homeostasis observed in GAPO syndrome. The five isoforms of Antxr1 are expressed in various tissue types and have been implicated in mediating cell adhesion, migration, and spreading via interaction with extracellular matrix (ECM). In mice, deficiency of ANTXR1 results in skin, vascular, and bone tissue abnormalities which can be attributed to excess ECM accumulation. Particularly, Antxr1 null mice showed reduced bone density and thick osteoid layers with reduced mineralization compared to wild-type mice.

Our preliminary data propose a mechanistic insight behind the observed bone abnormalities. Levels of ECM proteins and their gene expression were altered in different cell populations within bones of Antxr1 null mice. Transcription and protein levels of osteocalcin and osteopontin, which are specific markers of bone organic matrix synthesis in osteoblast, were increased. In osteocytes, expression levels of Mepe and Sost that negatively regulate mineralization were increased, while the expression of a positive regulator of mineralization, Dmp1, was reduced. These altered levels of expression provide a mechanistic explanation for the thick osteoid layers with lack of mineralization in Tem8 null mice. Interestingly, despite the increased expression of negative regulators of osteoclastogenesis, Sost and Opg, these mice contained increased number of osteoclasts, which may suggest uncoupling of cross-talk between osteoblast and osteoclast. However, it is unclear whether the observed abnormalities are due to the global or osteocyte-specific Antxr1 deficiency.

In order to investigate the role of osteocyte-specific Antxr1 deletion in mineralization, we have been using offspring mice from crosses between Tem8 fl/fl females with males expressing Dmp1-8.3 kb-Cre that preferentially targets osteocytes. First, we will use reporter mouse line TdTomato;Dmp1-8.3 kb-Cre to confirm the specificity of DMP1 expression to osteocytes. We expect TdToma fluorescent signal to localize preferentially in osteocytes. Tissue sections of various organs—liver, kidney, bone, and muscles—have been collected and will be studied by immunofluorescence. Once DMP1 expression is evaluated, the phenotype of Dmp1Cre;Tem8fl/fl mice will be compared to that of global knock-out mice. Bone phenotype will be analyzed using X-ray, MicroCT analysis, von Kossa staining; in concert, transcript level of ECM components and osteocyte specific genes will be assayed.
Involvement of the mTOR pathway in Encephalopathy of Prematurity

Maya Harary
Harvard Medical School, Francis Weld Peabody Society, Class of 2018

Shenandoah Robinson, MD
Department of Neurosurgery
Boston Children's Hospital

Preterm birth (<37 weeks of estimated gestation age, EGA) is associated with significant rates of neurological injury, known as encephalopathy of prematurity. Social impairment, attention deficit and hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) occur in high prevalence in affected children. Past studies indicate that impaired sensory processing, which can result from defective development of thalamocortical connections, may underpin these deficits.

In a rat model of premature birth, rats are subjected to prenatal transient hypoxia-ischemia (TSHI) that mimics the brain injury associated with preterm birth at 25 weeks EGA. These rats later show impaired gait, novel object recognition and social interaction. Neuroanatomical studies indicate that TSHI injures a vulnerable population of neurons in the transient sublate that are known to guide the development of thalamocortical connections. Past studies in the lab show that both the neuroanatomical and behavioral phenotypes of this model are rescued by post-natal erythropoietin (EPO) treatment. It has been hypothesized that the molecular mechanism that underpins the neuro-protective effects of EPO is the activation of the mTOR (mammalian target of rapamycin) pathway which may be otherwise diminished due to injury. This pathway regulates growth and protein synthesis in the cells, and has specifically been associated with numerous aspects of neurodevelopment.

Using molecular biology techniques, namely western blotting and immunohistochemistry, we have probed into the activation of the mTOR pathway in cortical tissue at various stages of development. Data are currently being collected for post-natal day 2 (p2).
BMI as predictor of adverse outcomes with intravenous sedation during surgical abortion

Gillian Horwitz
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Alisa Goldberg, MD, MPH
Department of Obstetrics and Gynecology, Brigham and Women’s Hospital
Director of Clinical Research and Training, Planned Parenthood League of MA

Approximately 1.1 million abortions were performed in the United States in 2011. Of these abortions, 94% occurred in an outpatient clinical setting. 77% of nonhospital abortions were surgical, and depending on the clinical setting, 40%-100% of first trimester and 80%-100% of second trimester patients received intravenous sedation. Intravenous sedation during surgical abortion improves pain control and patient satisfaction, yet some clinics restrict access to abortion for obese women, due to theoretical safety concerns about sedation in this population. It is unknown if these restrictions are warranted.

We are conducting a retrospective study of all women (n=26,679) who underwent surgical abortion with intravenous sedation at Planned Parenthood League of Massachusetts between September 1, 2010 and June 1, 2015 to determine if obese women experienced increased rates of adverse outcomes with intravenous sedation compared to non-obese women. For our analysis, obese women will be stratified into three groups: Obese I (BMI =30-34.9), Obese II (BMI =35-39.9), and Obese III (BMI ≥40) and comparisons made between each category and non-obese women (BMI <25). Since serious anesthesia-related complications are rare, we will additionally compare surrogate markers of hypoventilation and over-sedation including administration of supplemental oxygen and reversal agents. Using administration of supplemental oxygen as our primary outcome, assuming a baseline rate of oxygen utilization of 0.175% among non-obese women, an alpha error of 0.017, and 80% power, we can detect a 1% increase among obese I patients and a 2% increase among obese II and III patients.

Preliminary data reveal that during the study period, 55 patients (0.21% of the study population) required supplemental oxygen and 29 patients (0.11%) required reversal agents. An additional 33 women (0.12%) experienced vasovagal reactions. The remaining complications deemed probably anesthesia-related included anxiety (n=4), psychotic reaction (n=1), drug reaction (n=1), asthma attack (n=2), and seizure (n=2). Two of these patients (0.007%) required hospital transfer or hospitalization. Analysis comparing complications by obesity group is ongoing.

These preliminary results indicate that intravenous sedation for abortion in an outpatient clinical setting is extremely safe. Yet, we may lack adequate sample size to detect a clinically relevant difference in rare adverse outcomes between normal weight and obese women. Other limitations include, use of surrogate outcomes and variability in the documentation quality in the medical record. However, even if the rate of sedation-related complications is higher in obese women, if the absolute rate is exceedingly rare, BMI-based restrictions on intravenous sedation may be unnecessary.
A Single Center’s Experience with Donation of Facial Allografts for Transplantation

Anne Huang
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

Bohdan Pomahac, MD
Center for Reconstructive and Restorative Surgery Research
Division of Plastic Surgery, Brigham and Women’s Hospital

Face transplantation offers superior functional and aesthetic outcomes compared to conventional reconstruction, thus improving social reintegration and quality of life in patients with severely disfiguring injuries. With increasing clinical experience, it becomes important to optimize criteria to match donors and recipients in order to improve recipient outcomes and possibly facilitate consent to facial allograft donation. However, the available literature regarding donor procurement and matching in face transplantation is limited to a few case reports.

The face transplant team at the Brigham and Women’s Hospital describes its experience with donor facial allograft matching and procurement for 7 face transplants performed since 2009.

Important considerations for donors of facial allografts include type of death, allograft ischemia time, demographics, immunologic compatibility, serology, and post-procurement plans for facial restoration. We have historically procured facial allografts from brain-dead, heart-beating donors because their hemodynamic stability facilitates the logistics of donor procurement. We recruit donors that are within 1-2 hours of commercial flight and up to 2 hours of land travel, allowing time to prepare, flush, package, transport, unpack, and re-anastomose the donor facial allograft in under 4 hours.

Face transplantation is unique in that donor and recipient should be matched in gender and physical appearance. Relevant donor demographics include similar age, comparable skin tone/texture, and body mass index (BMI). However, there are no set guidelines on how to optimize the matching of appearance, and all 7 matches at our institution have been done at the discretion of our lead surgeon.

Immunologic compatibility requires ABO compatibility, suitable HLA typing, and negative crossmatch. Donor serology for infectious diseases, especially cytomegalovirus (CMV) and Epstein-Barr virus (EBV), is important because of the intense immunosuppression that patients must undergo after transplant. Three of our patients who were CMV seronegative received facial allografts from CMV seropositive donors and experienced primary CMV infection several months after transplant. High-risk CMV and EBV matches (donor positive/recipient negative) should be avoided when possible. Finally, donor facial restoration with a prosthetic mask or similar should be performed to preserve the dignity of the donor and the donor’s family.

Although every face transplant recipient has unique needs, we hope this report will help other face transplant centers and contribute necessary information to eventually establish a standardized set of donor characteristics that can be incorporated in a national face transplantation donor registry.
Somatic Genetic Biomarkers of Bevacizumab Response in Glioblastoma Multiforme

Jaeho Hwang
Harvard Medical School, Francis Weld Peabody Society, Class of 2018

Rameen Broukhim, MD, PhD
Department of Cancer Biology
Dana Farber Cancer Institute

Background: Bevacizumab (BEV) is the standard therapy for recurrent glioblastoma multiforme (GBM). Although it may not cross the blood-brain barrier to reach tumor cells, patients often have radiologic and symptomatic responses to BEV, and some exhibit prolonged responses.

Objectives: We hypothesized that response is determined in part by the genetic profile of the GBM. Consequently, we aimed to discover novel genetic predictors for BEV response, which would enable us to identify patients most likely to respond to treatment.

Description of Project: 139 adult GBM patients who have been treated with BEV at the Dana Farber Cancer Institute between 1998 and 2015 were examined. Mutations in approximately 300 genes of the OncoPanel assays, and copy-number variations genome-wide at 1-million loci through array Comparative Genomic Hybridization (aCGH) OncoCopy assays were screened for each patient. The two, analyzed measures of treatment response were time-to-progression and first follow-up MRI response. Time-to-progression was defined as the length of time between the first day of receiving BEV and the date on which further progression of disease was detected. The first follow-up MRI was performed between one and two months after starting BEV treatment, and response was defined as one of three categories, partial response (PR), stable disease (SD), or progressive disease (PD).

Results: Fisher’s exact tests for OncoPanel data and time-to-progression revealed eight, significant genes after false discovery rate correction: ERCC5, EGFR, SF3B1, IDH1, PTEN, TP53, BLM, and PRKDC (p-values < 0.05). In addition, the Cox-regression model for time-to-progression involving those genes was highly significant (p < 0.0001). (Hazard Ratio = exp(2.7134 \cdot ERCC5 + 0.1787 \cdot TP53 + 1.7512 \cdot SF3B1 + 0.3658 \cdot PTEN + 0.3519 \cdot EGFR – (1.6475 \cdot IDH1 + 1.1413 \cdot BLM + 1.0337 \cdot PRKDC). In addition, the OncoCopy data revealed amplifications of the 2p and 2q chromosomal arms in patients with PD at first follow-up MRI, compared to patients with PR or SD (q-values = 0.034).

Conclusion: Several, mutated gene and copy number variations have been found in relation to BEV response. Cox-regression analysis showed associations for longer time-to-progression with mutated IDH1, BLM, PRKDC, and shorter time-to-progression with mutated ERCC5, TP53, SF3B1, PTEN, and EGFR. Moreover, 2p and 2q chromosomal amplifications were significantly identified in patients with progressive disease.

Limitations: Some mutations in ERCC5 and BLM have been reported to be germline mutations with allele frequencies greater than 0.001. Thus, these genes may not have as much impact as implicated in the OncoPanel analyses.
The Implications of TMPRSS2:ERG Fusion Status In Prostate Cancer

Masis Isikbay
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Lorelei A. Mucci, MPH, ScD
Department of Epidemiology
Harvard T.H. Chan School of Public Health

Prostate cancer poses a serious health concern given that it is the most common cancer diagnosed in men. While much work has been conducted to help treat patients with prostate cancer, the dynamic nature of the underlying disease biology has proven difficult to elucidate. Unlike colon or breast cancer, there are no confirmed molecular subtypes of the disease. There is intriguing evidence to suggest that the common somatic event TMPRSS2:ERG may help further characterize the underlying pathobiology for a subset of prostate cancer. This common gene fusion is a combination of the transmembrane protease serine 2 (TMPRSS2) and the ETS-related gene (ERG) oncogene. An estimated 50 percent of men’s prostate cancers harbor this gene fusion, translating to more than 100,000 US men diagnosed each year with TMPRSS2:ERG fusion positive prostate cancer.

We undertook a study within the Physicians’ Health Study and the Health Professionals Follow-Up Study cohorts. These men have been followed for cancer incidence and mortality for more than three decades. We leveraged a prostate tumor repository in the cohorts in which many of the prostate cancer cases have been analyzed for the presence of the TMPRSS2:ERG fusion, and also have whole genome mRNA expression profiling data. We aimed to investigate whether there were unique genes and molecular pathways associated with the TMPRSS2:ERG fusion. Using gene set enrichment analysis, we were able to detect molecular pathways that were differentially expressed between fusion positive and fusion negative prostate cancer tumors. We discovered that many pathways (including ones responsible for glucose, fatty acid, and drug metabolism) significantly changed (FDR-q value <0.25) based upon fusion status. We previously showed that body mass index was positively associated with prostate cancer mortality among men whose tumors harbored the TMPRSS2:ERG fusion. In stratifying our samples by body mass index (BMI) values, we revealed that gene expression changes relative to fusion status depended upon the BMI of the patient population. Even within the same gene set, different expression enrichment patterns (comparing the fusion positive and negative cancers) were observed for healthy weight patients (BMI<25) and overweight/obese patients (BMI≥25).

In sum, these data support the hypothesis that the TMPRSS2:ERG fusion status could potentially serve as a biomarker for unique forms of prostate cancer that could benefit from tailored therapies in the future. Moreover, the BMI of the patient could further serve to dictate the disease biology and might be of clinical importance as well.
The Role of Recovery Coaches in Community-Based Treatment of Substance Use Disorder

Helen E. Jack
Harvard Medical School, Walter Bradford Castle Society, Class of 2018

Sarah E. Wakeman, MD
Department of Medicine
Massachusetts General Hospital

Approximately 23 million people in the US suffer from a substance use disorder (SUD). Nationwide, hospitalized patients with SUD cost more per admission and are more likely to be readmitted than patients without SUD with the same diagnoses.

Massachusetts General Hospital (MGH) recently hired five recovery coaches, individuals who are in recovery and connected to the local community, to work with the inpatient addiction consult team and primary care practices. When patients are identified as having an SUD, providers refer them to a coach who supports their recovery and helps them navigate healthcare and social services. Despite the introduction of coaches into SUD treatment programs nationwide, there is limited evidence about their efficacy or how they affect patients.

We are conducting in-depth interviews with five coaches and twenty of their patients to understand their perspectives on how coaches affect patient recovery and fit into the care team. We purposefully selected patients, seeking variation in gender, location, and number of contacts with a coach. To analyze the interviews, we are developing a code list using grounded theory principles. Two researchers will separately code each interview using the code list and reconcile differences through discussion. The final code assignments will guide analysis and presentation of themes. Qualitative methods are appropriate because factors affecting recovery and care team dynamics can be complex and best explored through the detail that in-depth interviews provide.

Findings to date indicate that patients and coaches perceived that coaches serve patients most effectively when they are available at any time to talk with patients and use personal connections to help patients access SUD treatment. Patients who chose to work regularly with a coach did so because the coach took time to get to know them, was more accessible than their physicians, and did not look down on them. Most coaches said their greatest challenge was working with physicians, who were not always open to hearing their opinion about a patient’s needs.

This is one of the only studies to evaluate a recovery coaching intervention for SUD and the first to use qualitative methods. The findings may inform the development of the MGH recovery coach initiative and the structure of future peer coaching programs. Understanding patient views on a new intervention helps ensure that the intervention is patient-centered—responsive to patient needs and achieving outcomes that matter to patients. As this was an exploratory, qualitative study, larger quantitative studies are needed to test hypotheses generated.
Association between Birth Weight, Fine Particulate Matter (PM$_{2.5}$) & Meteorological Factors

Otana Jakpor  
Harvard Medical School, Frances W. Peabody Society, Class of 2018

Joel Schwartz, PhD  
Department of Environmental Health, Department of Epidemiology  
Harvard T. H. Chan School of Public Health

Intrauterine growth restriction, the failure of a fetus to reach its growth potential, contributes significantly toward perinatal morbidity and mortality. Since the prenatal period is a critical time for development, certain maternal exposures during pregnancy can interfere with fetal growth. These may include meteorological conditions that can contribute to heat stress, such as temperature and humidity, and pollutants such as fine particulate matter (PM$_{2.5}$). However, literature on PM$_{2.5}$ effects remain limited, current evidence regarding temperature is somewhat mixed, and little is known about the effects of humidity on birth weight. It is important to understand the potential impacts of these exposures, especially in the face of climate change.

We analyzed birth data from two French mother-child cohorts, EDEN and PELAGIE. Our first objective was to assess the relationship between temperature and humidity and birth weight. This has already been studied within this population using temperature measurements from nearby monitors. However, we used a more refined estimate based on a temperature exposure model using satellite data with a fine (1 x 1 km) spatial resolution. We then compared the results obtained with the two strategies. Our second objective was to analyze the relationship between maternal exposure to PM$_{2.5}$ and birth weight, using PM$_{2.5}$ estimates from the same type of model as for temperature, based on high-resolution aerosol optical depth satellite data.

For Objective #1, we found the results of linear models using satellite-based temperature estimates to be largely consistent with those using measurements from nearby temperature monitors. This attests to the usefulness of satellite-based models, especially in settings with few monitoring stations. There was a positive association between birth weight and mean temperature in the first trimester, but a negative one in the third trimester. There was also a negative association between birth weight and mean relative humidity over the course of the entire pregnancy and in the second trimester.

For Objective #2, we found that PM$_{2.5}$ exposure in the second trimester was associated with a borderline significant increase in birth weight. This was surprising, since the suspected biological mechanisms of PM$_{2.5}$ exposure would generally lead one to expect the opposite effect, if any. We are currently working to characterize this data more fully, in hopes of clarifying this result.
Asthma is the most common chronic disease of childhood in the US, affecting more than 15% of children living in urban areas. Every year, asthma accounts for over 10 million missed school days and is the leading cause of school absences in the US. Urban minority populations experience greater asthma morbidity and have higher asthma-related mortality rates, with no signs of abating.

Prior studies on home-based environmental interventions using High Efficiency Particulate Air (HEPA) cleaners have resulted in reduced particulate pollutant exposures and improved asthma symptoms in children. School children on average spend 7-12 hours a day in school. Therefore, indoor air pollutants in schools can be a significant source of exposure for children. As less is known about the school environment, we piloted a classroom-based air cleaner intervention to reduce air pollutants in classrooms.

In a pilot randomized controlled trial, 25 children with asthma aged 6-10 years were enrolled from 3 urban US schools and randomized to the air cleaner (n=13, 9 classrooms) and control group (n=12, 9 classrooms). Classroom air pollutant measurements and spirometry were completed at baseline and twice after randomization during the academic school year. Asthma symptoms were surveyed every 3 months.

At baseline, classroom levels of fine particulate matter (PM$_{2.5}$), black carbon (BC), and nitrogen dioxide were 6.1 μg/m$^3$, 0.43 μg/m$^3$, and 13.6 ppb, respectively. The air cleaner intervention decreased PM$_{2.5}$ levels by up to 2.3 μg/m$^3$ (95% confidence interval (CI): -3.5, -1.0; p=0.003) and BC levels by 0.17 μg/m$^3$ (95% CI: -0.32, -0.03; p=0.03). These reductions corresponded to a 49% decrease in PM$_{2.5}$ and 58% decrease in BC concentrations. Nitrogen dioxide levels remained unchanged. Among spirometry findings, the air cleaner intervention improved peak expiratory flow by up to 16% (or 0.5 L/s; 95% CI: 0.1, 0.8; p=0.03). There was suggestive evidence of greater decreases in asthma symptoms in the air cleaner group.

In our pilot classroom-based air cleaner intervention, significant reductions were observed in particulate pollutants. Further large-scale studies are needed to comprehensively evaluate the effectiveness of school-based environmental interventions in reducing asthma morbidity in children.
Impact of a Dental Team on Documentation of Oral Health Findings among Patients in a Student-Faculty Collaborative Clinic

Yisi Ji
Harvard School of Dental Medicine, Francis Weld Peabody Society, Class of 2018

Lisa Simon, DMD
Harvard School of Dental Medicine, Department of Oral Health Policy and Epidemiology

Low-income populations are vulnerable to poor oral health and are more likely to visit a primary care provider than a dentist. However, integration of dental care into primary care clinics remains a challenge. The Crimson Care Collaborative at MGH-ChelseaHealth Center (CCC Chelsea) is a student-faculty collaborative clinic that provides primary care to this population in Chelsea, Massachusetts. Starting in June 2014, a dental team consisting of a dental student and attending dentist have been present for each weekly clinic session. The dental team serves as a consult service for oral health findings and provides training in oral health screening and education for medical and nursing student clinicians, who are trained to document oral health findings in clinic encounter notes. This was a retrospective chart review assessing the impact of this dental team present on the frequency of oral health documentation in chart notes. Oral health documentation rates from June 2013 to June 2014, prior to the dental team, were compared to rates after introduction of the dental team. Documentation of the oral exam increased from 11.88% to 50.50% of encounter notes after implementation (p<0.0001, Fisher’s Exact test, N=202). Incidental oral health findings were noted in 2.97% prior to the dental team’s implementation and 18.81% after implementation (p<0.0001). Student clinicians were also instructed to ask patients if they had previously visited the dentist in the past year as part of a standardized oral health screen, which was noted in 15.45% of all patient encounter notes, indicating that despite the presence of a dental team, there are still challenges to incorporating oral health screening into clinic visits. These results suggest that collaborative teams of different health professions spanning medicine, dentistry, and nursing can improve oral health awareness. Nursing and medical students were able to detect oral findings. Provision of direct dental care and improving oral health training for primary care providers are additional mechanisms currently being explored to improve care.
Identifying Factors Related to the Adoption and Sustained Use of Consumer Activity Tracking Devices and Applications

Manjinder Singh Kandola
Harvard Medical School, William Bosworth Castle Society, Class of 2018
Center for Primary Care Research Fellowship

Timothy Hale, PhD
Partners Connected Health Innovation

The recent surge in Connected Health technologies presents exciting potential to transform the health care landscape, ultimately by motivating lifestyle changes and increasing provider access while efficiently reducing incurred costs. However, the positive effect on health outcomes and improved care is challenged by the limited and transient adoption of these devices, which necessarily require sustained use to exert their intended effect. Indeed, little is known about the factors associated with the adoption and sustained use of consumer activity trackers or the barriers that limit the effectiveness of these devices in people’s efforts to improve their health. We hypothesize that precise consumer factors are predictive of preferences towards and sustained usage of particular technologies, and identification and automated guidance can effectively promote consumer usage to maximize positive health benefits.

At onset, participants (n=25) were assisted with the purchase and setup of a FitBit tracker through a version of the Wellocracy website created for the study and that provided guidance on the selection of an activity tracker. In addition, participants were provided one-time suggestions of increased step goals. Participants were continually monitored for uploading of tracker data, and were otherwise prompted through text messaging or over the phone. At the termination of the study, participants were asked to complete surveys as well as participate in one-on-one closeout interviews.

Extensive interviews and qualitative coding methods (n=15) revealed numerous insights into the barriers to using activity trackers and the need to create simple and easy to use solutions. Barriers included trouble uploading tracker data to cloud-based systems, device compatibility, poor tracking accuracy, loss of devices, travel away from home, and financial burden. More notably, they revealed persistent barriers to increased physical activity more generally, including sedentary lifestyles at home, poor health, and low social support. Interestingly, we also uncovered potential means of overcoming these barriers, including interventions to increase participants’ motivation, encouraging tangible feedback, making use of the “sentinel effect”, and lifestyle integration. Surprisingly, the trackers were also able to provide participants with a sense of control over physically disabling conditions while also engaging highly active users, indicating their broad spectrum of utility.

This study ultimately reinforced the idea that activity trackers can have significant benefits on an incredible range of participant types, albeit on a limited sample. We elucidated several barriers to adoption and sustained use, as well as specific ways in which these barriers can be overcome. We believe that adaptive messaging would not only amplify these positive effects of trackers, leading to sustained use, but also leverage their applicability to such a broad audience through personalized messaging. A well-designed algorithm may hold the key to unlocking the true potential of activity trackers.
Predictors of post-operative infections in neurological surgery: analysis of 94,000 patients

Aditya V. Karhade
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2019

Timothy R. Smith, MD, PhD, MPH
Cushing Neurosurgical Outcomes Center, Department of Neurosurgery
Brigham and Women’s Hospital

The ACS National Surgical Quality Improvement Program (NSQIP) database is a large, randomized, multi-center initiative to improve 30-day post-operative complication rates. Reduction of post-operative infections in neurological surgery can improve outcomes, decrease postoperative length of stay, and lower costs. We analyzed demographics, past medical history, and post-operative infections of 94,546 patients undergoing neurological surgery from 2006 to 2013.

5062 (5.4%) neurosurgical patients, with a mean age of 60.51 years, developed post-operative infections from 2006 to 2013. 553 (10.9%) had a past medical history of diabetes, 1170 (23.1%) were current smokers, 473 (9.3%) had pre-operative sepsis, 21 (0.4%) had pre-operative pneumonia, and 263 (4.8%) had pre-operative open wounds or wound infections.

The rate of post-operative infection of any type decreased from 8.3% in 2006 to 5.4% in 2013 (p < 0.001). 810 (16.0%) patients developed superficial surgical site infections post-operatively, 505 (10.0%) developed deep incisional surgical site infections, and 418 (8.3%) developed organ space surgical site infections. The types of infections and complications included urinary tract infections (1809 patients, 35.7%), pneumonia (1324 patients, 26.2%), sepsis (1131 patients, 22.3%), and septic shock (419 patients, 8.3%). The rate of superficial surgical site infections (p = 0.004), organ space surgical site infections (p<0.001), pneumonia (p<0.001), urinary tract infections (p<0.001), sepsis (p<0.001), and septic shock (p<0.001) each decreased significantly from 2006 to 2013.

Multivariate analysis controlling for gender, age, race, inpatient/outpatient status, diabetes, smoking, sepsis, current pneumonia, open wound/wound infection, and year of operation demonstrated that prior sepsis (p<0.001, OR=0.556), current pneumonia (p=0.037, OR=2.796), open wound/wound infection (p=0.004, OR=6.633), dependent functional health status prior to surgery (p<0.001, OR=1.668), ventilator dependence (p<0.001, OR=3.073), history of severe COPD (p=0.001, OR=1.486), impaired sensorium (p=0.027, OR=1.928), hemiplegia (p<0.001, OR=1.469), CVA/stroke with neurological deficit (p<0.001, OR=1.876), CVA/stroke without neurological deficit (p<0.001, OR=1.894), paraplegia (p<0.001, OR=1.631), quadriplegia (p<0.001, OR=2.512), steroid use for chronic condition (p=0.012, OR=1.289), and prior operation within 30 days (p<0.001, OR=1.645) were each significant predictive factors for developing post-operative infections after neurosurgery.

Our analysis indicates that neurosurgery patients with prior sepsis, current pneumonia, open wound/wound infection, dependent functional health status prior to surgery, ventilator dependence, history of severe COPD, impaired sensorium, hemiplegia, CVA/stroke with or without neurological deficit, paraplegia, quadriplegia, steroid use for chronic condition, and prior operation within 30 days are at increased risk for developing post-operative infections.
Characterization of Hydrocephalus and its Neurosurgical Interventions in Arusha, Tanzania

Andrew Ikhyun Kim
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Benjamin C. Warf, MD
Department of Neurosurgery
Boston Children's Hospital

The global burden of hydrocephalus is variable but significant. In developed countries, it is one of the most common congenital birth defects, affecting one in 500 births. Neonates in low-income countries face an additional risk due to post-infective hydrocephalus. In sub-Saharan Africa (SSA) alone, the incidence of hydrocephalus is 100,000 to 375,000 cases annually. Traditionally, ventriculoperitoneal shunt (VPS) placement has been the major intervention to alleviate this burden. More recently, Endoscopic Third Ventriculostomy with Choroid Plexus Cauterization (ETV/CPC) was introduced as a low-cost alternative. However, data on the global burden of hydrocephalus and its neurosurgical interventions remains limited and locally specific.

The specific aim of this study is to characterize hydrocephalus and its treatment in Arusha, Tanzania. Based on data from Uganda, we hypothesized that a post-infectious etiology of hydrocephalus would constitute a significant (>30%) portion of hydrocephalus cases and that ETV/CPC would provide improved postsurgical outcomes compared to VPS. Finally, we aimed to discover any pertinent patient variables that might indicate one surgery over the other.

Our methodology involves combination retrospective/prospective cohort study. We retrospectively collected pertinent data from two years of hydrocephalus patients (n = 175) who underwent VPS at Arusha Lutheran Medical Center (ALMC), a major referral center for hydrocephalus in Tanzania. This year, ALMC will begin implementing ETV/CPC, and we will prospectively collect two years of hydrocephalus patients who undergo ETV/CPC.

Pertinent variables include: etiologies of hydrocephalus, age and demographics at treatment, severity of disease (approximated by head circumference), numbers of patients, 30-day operative mortality, rates of shunt failure (based on Kaplan-Meier method), shunt infection rate (Kaplan-Meier), and percent lost to follow-up. We will run a logistic regression to identify variables that significantly effect outcomes.

I am currently working on preliminary analysis to break down the etiologies of hydrocephalus into post-infectious, congenital idiopathic, spina bifida, and unknown or post-hemorrhagic. Subsequently, I will conduct the surgical outcomes analysis and logistical regression.

The study is limited by selection bias ALMC is privately run and better funded than many hospitals in Tanzania. At this point, the dissemination patterns of the ETV/CPC procedure and of neurosurgical capacity in low- and middle-income countries precludes the possibility of a representative sample of hospitals.

Overall, the characterization of hydrocephalus etiologies and surgical outcomes analysis for its interventions will provide valuable information to influence future treatment and prevention of hydrocephalus.
Medication Related Osteonecrosis of the Jaw: Effect of Acidic Milieu on Osteoclast Function

John Klecker
Harvard School of Dental Medicine, Francis Weld Peabody Society, Class of 2018

Sven Otto, MD, DDS
Ludwig-Maximilians-Universität
Munich, Bavaria

Medication Related Osteonecrosis of the Jaw (MRONJ) has been reported in patients receiving either bisphosphonates or the antibody denosumab for oncological therapy. A diagnosis of MRONJ must include the exposure of necrotic bone in the oral cavity within 8 weeks of initiating therapy with no recent history of radiation to the jaw. Both bisphosphonates and denosumab work by inhibiting osteoclast function and therefore the bone remodeling process, but they do so by vastly different mechanisms. Bisphosphonates inhibit critical metabolic pathways in osteoclasts while denosumab specifically targets the RANK/RANKL signaling system, affecting osteoclast activation and proliferation.

The pathomechanisms leading to osteonecrosis of the jaw are unknown and central questions of paramount importance remain unanswered. The onset of MRONJ frequently occurs after oral trauma leading to the hypothesis that the acidic milieu present during an immunological response plays a key role. In order to further understanding of MRONJ, it is advantageous that the common mechanism connecting both bisphosphonates and denosumab to MRONJ be derived. Therefore, the aim of this study was to investigate the effects of bisphosphonates on osteoclasts and compare the results with those of denosumab focusing specifically on the RANK/RANKL system.

The effect of two bisphosphonates, Zoledronate and Ibandronate, on osteoclasts was tested at different concentrations and pH values. TRAP staining was used to qualitatively assure the differentiation of monocytes to osteoclasts. Cell viability and activity was analyzed by WST-1 assay and cells were counted using Hoechst-staining and mosaic imaging.

Both bisphosphonates revealed significant differences from the control at the varying concentrations and pH values. Zoledronate and Ibandronate showed a dose- and pH-dependent cellular toxicity with increasing concentrations of both bisphosphonates and lower pH medias. There was also a decrease in cell viability and activity (p<0.01), with more pronounced effects for Zoledronate. The equivalent assays using denosumab have yet to be performed.

We conclude that high concentrations of bisphosphonates and local acidic milieus, as commonly present in infections of the jaw, might play a key role in the pathogenesis of MRONJ in patients receiving bisphosphonates. When the same assays are performed with denosumab, we hope a common underlying mechanism leading to MRONJ can be delineated.

Margaret D. Krasne
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Katherine Semrau, PhD, MPH
Director, BetterBirth Program, Ariadne Labs
Associate Epidemiologist, Division of Global Health Equity, Brigham and Women's Hospital

Childbirth-related mortality is an alarming global public health concern with 350,000 maternal and 3.1 million newborn deaths worldwide each year. While previous efforts have improved access to facility-based deliveries, poor quality of care remains a major problem. To address the crisis of poor quality, the World Health Organization (WHO) created the Safe Childbirth Checklist (SCC), a 29-item tool consisting of evidence based essential birth practices (EBPs) that decrease maternal and child harm. BetterBirth, an ongoing adaptive intervention trial in Uttar Pradesh, India, seeks to determine the effectiveness of SCC through a peer-coach intervention. An essential component of the intervention is categorization of barriers to uptake based on the Opportunity-Ability-Motivation (OAM) framework. Initially conceived of as a tool to understand consumer behavior, OAM has been applied to many fields, including health. A mixed methods analysis was performed to elucidate the utility of OAM in identifying barriers to SCC item uptake and catalyzing generation of solutions that resolve barriers and improve birth attendant performance.

Peer-coaches collect data using the Observation Tool to Inform Support (OTIS) and Coach Support Tool (CST). Using quantitative OTIS data, overall descriptive statistics were reported and stratified by site to examine EBP failure rates (#EBPs completed/#EBPs observed) and associated barriers. Run charts were created for EBP uptake and OAM. Logistic regression analysis was performed to understand EBP uptake and OAM reporting over time. CST data was used to explore approaches to problem-solving over time.

Over 23 weeks in five intervention sites, 418 births were observed using OTIS (7,659 EBPs). The EBP failure rate declined from 16.4% in the first fortnight to 7.5% in the last fortnight ($R^2 = 0.46, p < 0.0001$). The most frequently reported barrier types were opportunity and motivation (54.4% and 30.3% of total reported barriers, respectively). The declining failure rate can be attributed to reduction in motivation and opportunity barriers. Supplies represented a small percentage of overall barriers (12.4%) and did not change meaningfully over time. Qualitative CST data included a set of solutions developed by coaches to resolve barriers. Limitations to the study include subjectivity inherent to data collection tools and variations in EBPs by barrier type.

OAM has proven an invaluable tool in this setting. It elucidates barriers to SCC uptake, highlights the impact of coaching intervention over time, and spurs improvement in the adaptive trial’s intervention. Future work will consider the value of OAM across 60 sites.
Magnetic Resonance Spectroscopy of Mild Traumatic Brain Injury and Posttraumatic Stress in the Military

Joshua R. Ladner
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

Alexander P. Lin, Ph.D.
Center for Clinical Spectroscopy, Department of Radiology
Brigham and Women's Hospital

Mild traumatic brain injury (mTBI) and posttraumatic stress (PTS) are hallmark injuries of Operation Iraqi Freedom and Operation Enduring Freedom. It is estimated that 11% - 28% of U.S. service members have sustained an mTBI and 10-18% experience PTS. mTBI and PTS are undetectable by traditional imaging methods and are traditionally diagnosed from the clinical presentation. Magnetic Resonance Spectroscopy (MRS) of the brain permits non-invasive interrogation to provide detailed chemical analysis of specific brain regions, which is unique from conventional magnetic resonance imaging.

In a prospective cohort study of US military service members we measured neurometabolite concentrations using MRS in four voxel regions; the posterior cingulate gyrus, anterior cingulate gyrus, parietal white matter, and left temporal lobe. Participants were divided into five categories based on their exposure status (mTBI only, PTS only, mTBI and PTS, Military Control, and Civilian Control). Five participants were assigned to each cohort. Cohorts were matched based on age, gender, and education level. The metabolite concentrations between the cohorts were compared using a paired t-test for initial exploratory analysis, followed by one-way ANOVA with Dunn’s test to account for multiple comparisons.

Our initial results show a unique spectrum for exposure cohorts, most noticeably in the posterior cingulate gyrus. In particular mTBI subjects show a decrease in total creatine (tCr), myo-inositol (Ins), glutamate and glutamine (Glx), and total N-acetyl aspartate (tNAA) when compared to military and civilian controls. Decreases in NAA, a putative marker of neuronal health, and decreases in glutamate, the primary excitatory neurotransmitter in the brain, are useful findings that correspond to the clinical presentation of mTBI. PTS subjects show a relative increase in total creatine (tCr), Ins, Glx, and tNAA when compared to military controls. Increases in glutamate are of particular importance as it corresponds to the clinical manifestations of PTS. Subjects with comorbid PTS and mTBI presented with a unique spectrum distinct from subjects with only mTBI and subjects with only PTS. Several significant results were discovered between the civilian controls and the exposure cohorts.

Initial data shows that MRS can elucidate unique neurometabolite profiles for military service members with mTBI or PTS diagnoses. The ability of MRS to distinguish small differences across many clinically useful neurometabolites will allow us to develop a clearer and quantifiable measure of mTBI and PTS.
Factors that motivate otherwise healthy HIV+ young adults to access HIV testing and treatment in Gugulethu, South Africa: A qualitative study

R. Frederick Lambert
Harvard School of Dental Medicine, Walter Bradford Cannon Society, Class of 2018
The Class of 1984 Scholarly Project Enrichment Fund Fellowship
Scholars in Medicine Award, The Center for Primary Care

Jessica Haberer, MD, MS
Center for Global Health, Massachusetts General Hospital
Department of Medicine, Harvard Medical School

In 2013, the World Health Organization (WHO) issued recommendations to expand antiretroviral therapy (ART) to include all HIV+ patients with CD4 count <500 cells/mm³, which will have important individual health benefits, as well as public health benefits through reduced secondary transmission of the virus. To help ensure the success of this treatment strategy, more information is necessary on how well otherwise healthy individuals access HIV testing and treatment. We conducted a qualitative study to better understand the motivations underlying the decision to access HIV testing, treatment and care among young adults residing in Gugulethu (a resource-poor township outside of Cape Town, South Africa with an HIV prevalence as high as 27%). We interviewed 25 HIV-positive individuals age 18-35 with WHO stage one disease (i.e., asymptomatic) and a CD4 count >350, who had recently started or made the decision to start ART. Using an inductive content analytical approach, we found that most individuals sought testing and treatment early in the disease progression because of a desire to appear healthy. HIV testing and taking antiretroviral therapy, if positive, would enable them to avoid the stigma associated with appearing ill, which most people in the community equate with AIDS. Many reported social support and/or a strong will to live that encouraged them to get tested for HIV as a means to stay healthy. A sense of normalcy, accessible healthcare services and a strong sense of trust also facilitated early treatment. Barriers included stigma associated with seeking HIV-related services and concerns about side effects of chronic antiretroviral therapy use. Elucidation of these obstacles was limited by the absence of a comparison group of participants who did not access testing or treatment for HIV. Understanding the factors driving otherwise healthy, HIV positive young adults to enter treatment could help in the development of interventions and policy change to increase the number of individuals on ART and, ultimately, reduce the rate of transmission.
Students as health coaches and change agents at Brookside Community Health Center: a tool to improve health outcomes in diabetic patients

Dalia Larios
Harvard Medical School, Oliver Wendell Holmes Society, Class 2018

Bevin Kenney, MD
Department of Adult Medicine, Brookside Community Health Center
Brigham and Women's Hospital

At Brookside Community Health Center, diabetes is the second most common diagnosis made by physicians in the adult medicine department. In 2013, a survey at this center found a subgroup of “high risk” diabetic individuals characterized by patients having an average of 11 medical diagnosis, 13 medical prescriptions, a BMI of 31.8, and an HbA1c of 8.1%. Given these findings, it was postulated that health coaching could be used as a tool by diabetic patients to improve health outcomes, self-directed goals, and self-management of their chronic disease.

The purpose of this study is to have student health coaches supplement routine clinical care of diabetic patients and identify high-yield coaching interventions that can be taught to current staff and integrated into the workflow at Brookside. The following specific aims are identified: **Aim 1:** Investigate what characteristics in the health of a diabetic patient—diet, physical activity, social support, and more—are reported by the patient to be most important to their health. **Aim 2:** Measure changes, if any, in diabetic care management, patient satisfaction with attainment of self-identified goals, behavioral changes, attitude toward health coaches, and relevant clinical markers (HbA1c, BMI, and blood pressure). **Aim 3:** Create a health coaching quality improvement assessment report for the Brookside medical team that can be used as a guide to implement sustainable curriculum changes at this site. In pursuing these aims, motivational interviewing techniques are being used by health coaches to guide diabetic patients with self-identified goals. A de-identified record is kept of patient goals, reflections, and outcome measures (HbA1c, BMI, and blood pressure) for data analysis. To evaluate behavioral changes in patients, a verified patient activation measure (PAM) questionnaire was administered at the commencement of the study and will be given at its conclusion.

In a three month period, patients have attended an average of 2-3 coaching sessions and responded positively to working with a health coach based on preliminary interview data. To date, most patients have identified (1) learning about diet (2) increasing physical activity, and (3) managing their depression/anxiety as their three most important health concerns. Currently, patients have more commonly achieved dietary goals over those in other areas of concern and reported several barriers, many which were unforeseen, to achieving desired health changes. Importantly, further analysis of outcome measures, narrative data, behavioral changes through the PAM questionnaire, and satisfaction reports is still needed to propose sustainable recommendations on this program.
Urinary biomarkers correlate with preoperative disease status, presence of transdural collaterals and predict 1-year angiographic outcomes in pediatric moyamoya patients

Alexandra Giantini Larsen
Harvard Medical School, Frances W. Peabody Society, Class of 2018

Edward Smith, MD
Department of Neurosurgery /Vascular Biology Program
Children’s Hospital Boston / Harvard Medical School

Moyamoya disease is an arteriopathy that is characterized by progressive stenosis of the intracranial internal carotid arteries, including the anterior cerebral arteries and middle cerebral arteries. The narrowing of these arteries results in brain ischemia and a compensatory development of new blood vessels. Resultant from the brain ischemia with inadequate compensatory mechanisms, moyamoya disease accounts for up to 6% of childhood ischemic strokes. Diagnosis of pediatric moyamoya requires imaging which include risks associated with anesthesia and angiography. Here we describe the novel application of non-invasive urinary biomarkers to assess preoperative ischemia, development of transdural collateral vessels and predict 1-year angiographic outcomes from preoperative samples.

Preoperative urine samples were collected from moyamoya patients (age<22 years). Radiographic data (Suzuki stage, presence/location of preoperative transdural collaterals and postoperative Matsushima grade) were performed by neuroradiologists and obtained from review of clinical records. Quantitative analysis of protein levels was performed with ELISA, normalizing for protein and subjected to statistical comparison between groups.

A total of 132 patients with moyamoya had samples and imaging for analysis. Urinary VEGF and netrin-1 levels were significantly elevated in moyamoya patients compared to matched controls (6.6 vs. 4.4pg/ug and 0.6 vs. 2.3pg/ug, p<0.05 respectively). In patients without transdural collaterals, VEGF and netrin-1 urinary levels were higher than in those with collaterals (n=68 without, 64 with, p= 0.03 netrin, NS VEGF) Higher preoperative urine levels of both VEGF and netrin-1 correlated with better postoperative Matsushima grade (n=38,29,16 for Matsushima A,B,C, p<0.01 for VEGF and p<0.05 for netrin-1).

Urinary levels of VEGF and netrin-1 are elevated in moyamoya patients and may correlate with an increased angiogenic drive that is higher in patients without spontaneous collaterals (who may be more ischemic than those who have already established collaterals) and whose presence may aid in development of surgical collaterals after indirect revascularization. These experiments provide proof-of-principle data that urinary biomarkers may have utility in augmenting clinical decision-making.
Perceptions of Rwanda's Medical Postgraduate Programs
Qualitative analysis of trainee and faculty perceptions of a medical education intervention

Claire Learmonth
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

Mark Corden, MD
Pediatrics, Children’s Hospital Los Angeles

Kim Wilson, MD, MPH
Pediatrics, Children’s Hospital Boston

In 2012, the government of Rwanda launched the Human Resources for Health (HRH) Program. HRH is an innovative medical education program that aims to dramatically scale up the number of healthcare workers in Rwanda over a 7-year period by enlisting US faculty to participate in resident-level training programs. An annual survey of medical residents in the University of Rwanda School of Medicine (URSOM) was initiated in 2013 as an indirect measure of the HRH program. Preliminary results were difficult to fully interpret given the short and quantitative nature of the survey tool. To further elucidate their perspectives, resident focus groups were conducted using the survey tool as a guide. In addition, focus groups were conducted with US and Rwandan HRH faculty to help elucidate resident responses to the survey and to gauge their perspectives of the program.

A total of six 90-minute focus groups were conducted: four with postgraduates and two with faculty. The focus groups were recorded and the responses were transcribed into the qualitative analysis software N-vivo. Going forward, the transcripts will be coded for salient themes and emerging patterns across all groups.

There are several potential limitations to this study. While participation in the focus groups was meant to be voluntary, recruitment methods differed by department. Therefore, some participants may have felt pressured to attend a focus group, and they might have felt less inclined to provide genuine answers. Furthermore, complete anonymity could not be guaranteed because of the small resident class sizes. To overcome this issue, informed consent was obtained, and it was reinforced that individual responses were not linked to any identifying information or demographic data. The small sample size will make it difficult to arrive at conclusions that might be applicable to other settings, meaning that the findings of these focus groups may not be generalizable to other institutions conducting health education interventions. Finally, cultural differences in responses to similar questions may mitigate against comparisons between different healthcare settings.

While data analysis is pending, we have demonstrated that it is possible to conduct a focus group study in a resource-limited setting using rigorous research methods to obtain much-needed qualitative data. Such data can inform in real time the policies and interventions of the ongoing HRH program to further enhance resident education and faculty experience. Next steps include integration of the results with survey data and dissemination of our findings to URSOM leadership and HRH stakeholders.
Proteomic Profiling to Elucidate Intratumoral Heterogeneity and Cancer Evolution in Lung Cancer

Charlotte Lee
Harvard Medical School, Irving M. London Society, Class of 2018

Franziska Michor, PhD
Department of Biostatistics and Computational Biology
Dana-Farber Cancer Institute

Tumors often display a high degree of intratumoral heterogeneity as manifested by dynamic changes in gene expression, protein expression, and on gross examination of histology, among many other features. Clinically, this underlying heterogeneity can drive tumor evolution and progression towards a more aggressive neoplastic state and a worse prognosis for patients; therefore, identifying the diverse composition of a tumor for early risk stratification is of critical importance.

To elucidate intratumoral heterogeneity and intracellular hierarchy in a novel manner, we first conducted a low-cost quantitative proteomics analysis using MALDI-TOF mass spectrometry on different histological regions of individual tumors from 35 lung cancer patients, as well as from 3 mesenchymal stem cell samples. This resulted in a total of over 1900 spectra collected across all patients with at least 29 spectra per patient. The histologies identified were acinar, basal cells, bronchial epithelium, lepidic, complex gland, micropapillary, near tumor normal, normal alveolar, papillary, papillary lepidic, papillary mucinous, and solid. Patient-specific information including survival status, sex, age, smoking status, SUV by FDG-PET scan, tumor size, EGFR, KRAS, and ERCC1 mutation status, among other variables was obtained. We then compared the proteomes derived from each tumor to the stem cell proteomes, and using computational strategies, mapped the distance of each histological sample from the mesenchymal stem cell state; using clustering techniques, we organized the major histological subtypes into a phylogenetic tree from stem cells to normal lung.

We hypothesized that by applying and improving upon map of tumor evolution based on the distance of each individual histological sample from a stem cell state. Apart from liquid tumors, there have thus far been limited studies on the prognostic significance of different subclones in solid tumors, and therefore we treated each histological sample as a subclone within each patient. We also aimed to identify survival-associated subclones and prognostic molecular signatures across combinations of subclones. Identifying these subclones may provide insight into malignant micrometastases to other organs. Using co-expression network analysis, we further pinpointed distinctive significantly dysregulated co-regulatory protein networks within each histological subtype. Based on these networks, we sought to identify important hub proteins within each histology. Ultimately, using proteomic profiling in solid tumors can be a novel approach in functionally characterizing intratumoral heterogeneity, and may allow for a more robust analysis of the diverse molecular expression of single tumor samples. Our results may help inform the field of targeted broad-scale proteomics profiling for therapeutic use.
Identifying a Role for the Posterior Temporal Lobe in Grammatical Processing

Daniel K. Lee
Harvard Medical School, Irving M. London Society, Class of 2018

Ziv Williams, MD
Department of Neurosurgery, Center for Nervous System Repair
Massachusetts General Hospital

Grammar plays allows us to seamlessly integrate and construct complex sentences based on abstract acquired rules. Here, we discover a distinct area within the posterior temporal lobe, immediately anterior to canonical Wernike’s area, in which inhibition leads to a selective disruption of correct grammatical processing without other speech deficits and identify the distinct spatiotemporal dynamic in which syntactic rules are encoded. Using prospective stimulation inhibition techniques as well as long-term retrospective evaluation of subjects with focal anatomical lesions, we find that the dominant mid-portion of Brodmann areas 21 and 22, is essential for syntactic processing without differentially affecting speech perception, semantic retrieval, articulation or monitoring. In addition, by using targeted high-resolution electrographic recordings from the same area, we identify the rapid temporal encoding of syntactic elements, relation to semantic context, morphology and grammatization. This study identifies an area within the posterior temporal lobe that is essential for normal grammatical processing.
Impact of Restorative Treatment on Oral Health-Related Quality of Life in Patients in Ireland with Hypodontia – A Two-year Follow-up Observation Study

Samuel Lee
Harvard School of Dental Medicine, William Bosworth Castle Society, Class of 2018

Finbarr Allen, BDS PhD MSc
Professor of Prosthodontics
Department of Restorative Dentistry
Cork University Dental School and Hospital

Hypodontia is the term used to describe the congenital absence of one or more teeth in the adult dentition. The prevalence of hypodontia varies among countries: Saudi Arabia - 2.6%, United States - 3.5%, and Ireland - 11.3%. The human dentition plays a critical role in one’s quality of life (QoL) and largely impacts systemic health (difficulty masticating) and psychological health (self-esteem). This can be problematic as an individual moves from childhood into adolescence and adulthood when teeth are missing.

There are limited data available on the subjective impact of hypodontia, or how restorative treatment impacts oral health related quality of life (OHRQoL). The primary objective of this study was to analyze the impact of restorative treatment using implant-retained prostheses on a patient’s QoL 24-months following placement of one or more single unit implant-retained prostheses. Secondary objectives were to analyze implant stability and crestal bone loss (CBL).

In this observation study, thirteen consecutively recruited patients (7 female, 5 male: age range 17-25 years) with congenital absence of teeth in the anterior maxilla who met inclusion criteria and participated in the study. All patients had completed a course of orthodontic treatment prior to the surgical and restorative phases of care. Pre-screening procedures included a detailed clinical examination (periodontal status, plaque and bleeding scores, and radiographs) and a discussion about treatment options. Patients also completed an oral health-related quality of life measure (OHIP-20) and provided written consent to participate in the study. Following placement of implants, (Straumann Roxolid™ Narrow Platform) implant stability was recorded using a resonance frequency analyzer (Ostell™) that measured implant stability quotients (ISQ). Standardized peri-apical radiographs were recorded at each data collection point to analyze crestal bone levels. Participants’ responses on the OHIP-20 questionnaire, CBL, and implant stability quotients (ISQ) were obtained at abutment connection, placement of the final restoration, 12-month, and 24-month post-treatment follow–up reviews.

The findings of this study show that patients had drastically improved OHIP scores at both 12-months and 24-months after treatment (p=.008 and p=.002, respectively), indicating substantial improvement in OHRQoL. The stability of the implants (n=21) had increased between time of placement and loading with final restoration measures (p<.0001) and minimal observed CBL (p≥.005).

Restoration of spaces with implant retained prostheses in patients with congenital absence of incisor and canine teeth had a positive impact on OHRQoL.

Acknowledgement: This study was supported by Straumann, Switzerland.
Evaluation of the Dental Vibe Injection Comfort System

Stephanie Lee
Harvard School of Dental Medicine, Francis Weld Peabody Society, Class of 2018

Jeffry Rowland Shaefer, DDS
Department of Oral and Maxillofacial Surgery, Harvard School of Dental Medicine

Managing pain during dental treatment is critical to a successful patient experience. Pain from local anesthesia injections can be reduced by distraction and counter-irritation techniques. The Dental Vibe Injection Comfort System (DV) was developed to lessen pain/discomfort through pulsed vibration, a form of counter-irritation.

Vibration of tissues near injection site can reduce pain perception through the gate control theory. Both pressure (A-beta) and pain (A-delta, C) afferents synapse onto interneurons in the dorsal horn. However, the circuitry of their distinct interneuron targets creates a gate that can limit the passage of pain signals: Interneurons activated by A-beta fibers serve to inhibit interneurons that relay pain information from A-delta or C fibers up the spinal cord. When pressure from vibration and pain from injection activate their respective receptors simultaneously, pressure impulses, which travel through larger, more thickly myelinated A-beta fibers, reach and activate their interneurons earlier. These interneurons ultimately inhibit the passage of pain impulses from unmyelinated C or lightly myelinated A-delta afferents.

Preliminary studies have shown DV’s efficacy in reducing discomfort from maxillary infiltration anesthesia. Our study's aims were to evaluate DV’s efficacy in reducing pain/discomfort from intra-oral long buccal (LB) and inferior alveolar nerve (IAN) injections and the time needed to achieve complete anesthesia during an IAN block. DV was hypothesized to reduce pain/discomfort during injections and the time to anesthesia.

Each subject received bilateral LB injections and an IAN block. Using block design, DV was randomly assigned to either the first or second LB injection and to thirty subjects on their third injection, the IAN block. After each injection, subjects rated their pain on a visual analog scale and discomfort, unpleasantness, and difficulty in enduring the injection on a modified symptom severity index.

Data was obtained from sixty subjects, equally split by sex, ages 21-32. Forty-five were predoctoral dental students, with the remainder medical/art/other. Subjects given injections with DV rated significantly less pain, discomfort, unpleasantness, and difficulty in enduring LB and IAN injections, regardless of whether DV was used on the first or second LB injection. Time to complete anesthesia was not significantly different when DV was used on IAN blocks.

These pilot results indicate that DV may reduce pain/discomfort during dental anesthetic injections. Limitations include the fact that many subjects were dental/medical students, familiar with performing and enduring injections. More studies are warranted on layperson populations.
Simulation of Paravalvular Leak (PVL) after Transcatheter Aortic Valve Replacement (TAVR)

Suk Joon Lee
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Elazer Edelman, MD PhD
Harvard-MIT Health Sciences and Technology
Brigham and Women's Hospital

The transcatheter aortic valve replacement (TAVR) is not only an essential treatment option for patients who are not eligible for open heart surgery but also a less invasive alternative to surgery for patients at high surgical risk. Despite this benefit, TAVR often causes paravalvular leak (PVL), a major complication shown to be associated with increased mortality.

The characterization of PVL caused by TAVR is needed to understand its effect on heart and to develop a better diagnostic device for PVL for treatment planning. The goal of this project was to investigate numerically how the presence of PVL following TAVR affects the flow-field characteristics during diastolic phase using computer simulation.

We generated idealized yet realistic computer 3D models of left ventricle, aorta, mitral valve, and transcatheter aortic valve using computer aided design software (Solidworks). Using these model geometries, we executed 3D flow simulation of PVL using a commercial simulation software (Fluent, Ansys). The simulation was run for the full period of diastole with dynamically changing pressure values, which were calculated through lumped parameter modelling, at both boundaries (aorta and mitral valve).

The simulation results on three different PVL severities (mild (PVL area < 5 mm²), moderate (10 < PVL area < 20 mm²) and severe (PVL area > 30 mm²)) show that the jets emerging from PVL orifices rapidly diverge within the LV. The speed of jets could reach up to 5.3 m/s for a total PVL area of 20 mm², consistent with the echocardiography results which found a peak PVL jet velocity of 5.2 m/s in a patient with a total PVL area of 20 mm². Also, the simulation result located high shear stresses on the TAV leaflets.

The diverging nature of the jets brings a significant implication that simple evaluation of the severity of PVL based on cross-sectional measurements of the jet might lead to significant errors. Also, the shear stress result demonstrates that altered flow condition leads to higher shear stresses on valve leaflets, which can cause rapid deterioration in the leaflets and reduce valve durability. This represents an important finding if TAVR is planned to be performed in younger patients.

The limitation of this study is not taking the movement of a left ventricle wall and the interaction between blood and tissue into account. To overcome this limitation, more complex fluid solid interaction (FSI) model must be developed in the future.
Characterizing the Response of a CDK Inhibitor Family to Anti-proliferative Stress

Howard Li
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Galit Lahav, PhD
Department of Systems Biology
Harvard Medical School

The cellular response to anti-proliferative signals is fundamental to cell cycle control. p21 is a CDK inhibitor (CDKi) shown to mediate cell cycle arrest in response to DNA damage—an important anti-proliferative stressor in cancer therapy. But while p21’s response to DNA damage is well-documented, relevant stressors besides DNA damage also exist. Moreover, p21 belongs to a structurally homologous family of CDKis that includes p27 and p57, but the regulation of p27 and p57 is less understood.

In this study, we sought to characterize the behavior of the entire p21/p27/p57 CDKi family under a variety of anti-proliferative stressors: DNA damage (neocarzinostatin), mTOR blockade (AZD8055), and serum starvation. Using quantitative PCR (qPCR) and immunofluorescence (IF), we measured p21/p27/p57 RNA and protein in MCF7 human breast adenocarcinoma cells under these conditions, sampling timepoints from 0 to 24 hours.

We find that while DNA damage does indeed cause rapid induction of p21, p27 is relatively unaffected and p57 shows a delayed but strong transcriptional induction at 24 hours. p57 protein levels, however, undergo transient oscillations as soon as 2 hours—a response that precedes p57’s transcriptional activation and thus implicates post-translational mechanisms in p57’s early response to DNA damage. Additionally, IF analysis of p57 reveals a shift from nuclear to cytoplasmic localization by 8 hours after DNA damage, perhaps also by a post-translational mechanism.

While p21 was largely unaffected by the other stressors in this study, p27 and p57 transcription were both strongly induced by mTOR blockade and serum starvation. Under serum starvation, these dramatic increases in p27 and p57 transcription were not matched in their protein abundance, indicating significant post-transcriptional regulation of p27 and p57 in the setting of serum starvation.

Finally, to examine how different anti-proliferative signals interact at the level of CDKis, we subjected MCF7 cells to combinations of anti-proliferative stress. We find that mTOR blockade enhances the transcriptional response of p21 to DNA damage. At the same time, while DNA damage does not affect p27 and p57 alone, it abrogates the effect of mTOR blockade on both these proteins. Both mTOR blockade and serum starvation individually produced striking responses in p27 and p57, but the combination of these stressors produced a dampened response.

Taken together, these results highlight the complexity of the p21, p27, and p57 response to anti-proliferative stress—particularly the role of post-transcriptional and post-translational regulation, and antagonistic and synergistic relationships between anti-proliferative signals.
Characterizing Molecular Pathways that Regulate Tumor Immune Resistance in Esophageal Adenocarcinoma

Kevin X. Liu
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Adam J. Bass, MD, MSc
Assistant Professor of Medicine, Division of Cellular and Molecular Oncology
Dana-Farber Cancer Institute

In recent years, rates of esophageal adenocarcinoma (EAC) in the United States and other Western countries have markedly increased, but EAC patients have a remarkably poor prognosis. Growing evidence suggests that many types of cancers co-opt immune checkpoint pathways, including the programmed cell death protein 1 (PD-1) pathway, to escape anti-tumor immune responses, and antibodies that block these pathways are emerging as promising therapies for various cancers. Molecular mechanisms underlying immune evasion in EAC have been, to date, subjected to little study. New research into this area carries great potential to facilitate the development of new immune-based therapies.

Given the promising nature of PD-1 pathway immunotherapy in other cancers, we hypothesized that EAC tumors utilize established immune checkpoints and other signaling pathways to regulate tumor immune resistance. To test this hypothesis, we first conducted tumor tissue microarrays to systematically examine expression of PD-1, and its ligands, programmed cell death ligand 1 or 2 (PD-L1 or PD-L2), in 354 esophageal adenocarcinomas. We found that 51.7% (n=183/354) of esophageal adenocarcinomas have moderately strong PD-L2 epithelial expression in at least one core. Work in the laboratory also described PD-L2 epithelial expression in 42.8% (n=9/21) of Barrett's esophagus (n=21) samples, and 0% (n=0/14) of reflux esophagitis samples. Thus, we next tested whether cytokines interleukin 4 (IL4) and interleukin 13 (IL13), which are up-regulated in the transition to Th2-predominant Barrett's esophagus, contribute to induction of PD-L2 expression. Interestingly, we found that treatment of EAC cell lines with exogenous IL4 and IL13 increased PD-L2 mRNA; however, knockdown of signal transducer and activator of transcription 6 (STAT6), a key regulator of IL4- and IL13-mediated Th2 response, does not affect PD-L2 mRNA expression. Next, we sought to further characterize the immune microenvironment of PD-L2-positive and -negative EAC tumors by analyzing EAC biopsies and surgical resection samples by immunohistochemistry and immune gene expression analysis using the NanoString nCounter system. We are currently analyzing the data to understand the populations of immune infiltrate and their spatial organization in EAC tumors, and investigate whether that PD-L2-positive and -negative EAC tumors contain different immune cell subpopulations that aid in acquisition of anti-tumor immunity. Taken together, these results suggest that immunotherapy may serve as a novel therapeutic strategy for EAC, and together with future studies, will provide great insight into the role of immune checkpoint pathways in EAC.
The Expansion of Digital Clinical Resources

Damir Ljuboja
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Rebecca Weintraub, MD
Global Health Delivery Project at Harvard University
Division of Global Health Equity, Brigham and Women’s Hospital
Harvard Medical School

Digital clinical resources (DCRs) are on- and off-line tools used in medical education and care delivery with the overarching goal of improved patient outcomes. Recently, there have been substantial increases in the prevalence of such platforms in both the developed world and in resource-limited settings.

However, there is an information gap regarding who is utilizing which tools, in what context, and what barriers restrict their use. The goal of this study was to develop an understanding of the differing landscapes for DCRs and to foster knowledge of how such resources may be expanded into regions in which they are currently underused or inaccessible. In doing so, stakeholders can identify and target these barriers more directly to improve education and patient care.

In order to achieve this objective, we conducted a weeklong “Expert Panel” via the Global Health Delivery Online platform to provide different lenses on this theme. Panelists were rigorously screened and recruited. During the panel, they were asked a series of daily questions and answered them based on their experience and the literature, along with commentary by 8,565 registered members over 125 posts.

As a case study, interviews were conducted in post-war Bosnia to determine the prevalence of DCRs and understand the health IT infrastructure in the region. During a two-week period, 38 healthcare professionals were interviewed across five medical centers. Of those interviewed, 2/38 (5.3%) use DCRs. 30/38 (78.9%) attribute the lack of DCRs to infrastructural insufficiency resulting from financial barriers and 37/38 (97.4%) emphasize the priority of an IT system.

These methods illuminated key barriers to the uptake of DCRs. In low resource settings, the primary barrier is lack of reliable infrastructure. Moreover, clinical guidelines are often formulated in the developed world, leaving little flexibility for application in developing countries. Research should be conducted to evaluate the needs of clinicians in different practice settings and subsequently be used to establish care guidelines in those regions; the end-user should be at the center of the development process.

Possible solutions hinge on fostering a culture of quality improvement to provide the basis for healthcare innovation. Collaboration is necessary between academics, physicians and governing agencies to construct a cohesive set of clinical guidelines. This will entail leveraging health data to perform analyses of treatment effectiveness, pharmacovigilance, and cost. Major effort and a paradigm shift are necessary, but many counties could see an improvement in DCR use and, resultantly, patient outcomes.
Barriers to Health for the Homebound III: Patients’ Perspectives

Tracy Lu
Harvard Medical School, Francis Weld Peabody Society, Class of 2018

Arash Mostaghimi, MD, MPA
Instructor in Dermatology
Brigham and Women’s Hospital

Approximately four million vulnerable adults in the United States are classified as homebound because they are frail, functionally limited, and have difficulty accessing health care services in physician offices or hospitals. Despite a growing homebound population and growing usage of home-based medical services, homebound patients are still a relatively invisible population from a quality and care delivery standpoint. Their inability to access normal modes of medical care, multiple chronic conditions, and functional and social challenges require a focus on a medical care delivery approach that is truly patient-centered and aware of their home environment. We aimed to increase the focus on quality improvement of care for homebound patients by using video ethnography to engage in a patient-centric, qualitative study of their lives and care experience.

We recruited patients from two local clinics that work with the homebound: Upham Corner’s Health Center and BWH Wound Care Center. Interviews were performed and filmed in the homes of the recruited patients to capture their natural living situation. Interviewers followed a predesigned interview guide containing open-ended questions in the categories of personal, homebound experience, health care, medications, and attitudes toward technology. Interviewers tried to capture patients “in action” by asking them to “show and tell” processes such as medication management or mobility challenges, striking a balance between following the interview guide and following patient cues that often revealed new themes and perspectives.

We interviewed a total of 17 patients of both genders, various ethnicities, and varying socioeconomic backgrounds, with a majority being of lower socioeconomic status. The two principal team members each independently coded the interviews from the 17 patients by watching the interviews and labeling overarching themes. The two coders then collaborated to reconcile any coding differences and to identify subthemes within each general theme. Finally, team members sorted, tabulated, and filtered the theme and subthemes to draw final conclusions about the most salient and actionable themes.

The interviews revealed that nearly half of the participants experienced housing instability, with a few facing imminent eviction. Wide disparities in health and homecare benefits received among the patients, irrespective of financial means, also emerged. In addition, the videos offer extremely powerful and poignant representations of these marginalized patients’ hopes, dreams, and challenges ranging from isolation to medication adherence. We are working towards creating a video documentary highlighting these findings to engender awareness and reform among clinics and advocacy groups.
Circulating Growth Differentiation Factor 11/8 Levels Decline with Age

Claudio Macias Trevino
Harvard Medical School, Irving M. London Society, Class of 2018

Richard T. Lee, MD
Department of Medicine
Brigham and Women’s Hospital

The growth differentiation factors 11 (GDF11) and 8 (GDF8) are members of the TGF-β family, and share 90% amino acid sequence homology. In addition, TGF-β cytokines are known to be involved in regulating proliferation, differentiation and other biological processes by activating the SMAD protein family. Recently, Egerman et al. reported decreasing levels of GDF 11 and GDF 8 in mouse serum as mouse age increases. In this study, we clarified the levels of circulating GDF11/8 as a function of age and investigated the effects of administration of exogenous GDF11 on the murine heart. We used western blot analysis to compare GDF11/8 levels in the serum of multiple mammalian species, including mice, rats, horses and sheep. We detected an age-dependent decline in circulating levels of GDF11/8 (~12.5 kDa band) with supporting data from mass spectrometry on mouse serum. Further, we showed that the ~25 kDa band identified by a monoclonal antibody that recognizes both GDF11 and GDF8 and shown by Egerman et al. to increase with age coincides with immunoglobulin G (IgG) light chain recognition. The 25 kDa band was significantly reduced after depletion of IgG from murine serum, but the 12.5 kDa band remained unchanged. Finally, we showed that exogenous GDF11 administration activated SMAD-2 and SMAD-3 signaling in myocardium and reduced cardiac mass in both young (2 month old) and old (22 month old) mice in a dose dependent manner over a period of 9 days. Thus, we demonstrated that multiple mammalian species exhibit decreased circulating levels of GDF 11/8 with increasing age and that exogenous GDF11 activates SMAD signaling and reduces cardiomyocyte size. Further investigation on the mechanism of this age-related decline could provide advances in understanding age-dependent cardiac pathologies.
Brain Activity Mapping in Tsc1 Mutant Mice to Identify Macrocircuit Abnormalities

Rebecca MacRae  
Harvard Medical School, William Bosworth Castle Society, Class of 2018  

Mustafa Sahin, MD PhD  
Boston Children’s Hospital, Department of Neurology  
F.M. Kirby Neurobiology Center, Center for Life Science

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by social interaction deficits, language difficulties, repetitive behaviors, and cognitive delays. The prevalence of ASD, severe impact on families, and large cost of care have identified ASD as a public health concern. Therapies based on neurobiological mechanisms underlying ASD could alleviate individual and societal burden of ASD. Complex neurobiological mechanisms have obscured progress in ASD research and inhibited treatment development. However, ASD have high heritability and high ASD comorbidity rates with simple-Mendelian disorders such as tuberous sclerosis (TSC), provide a model system for researching ASD neurobiological mechanisms.

TSC is a dominantly inherited disease caused by mutations in the \textit{TSC1} or \textit{TSC2} and resulting in benign tumor growth in multiple systems throughout the body, including the brain. Additionally, TSC individuals exhibit neurodevelopmental abnormalities that contribute to intellectual disability and high ASD comorbidity (up to 50%). The proteins encoded by \textit{TSC1} and \textit{TSC2}, hamartin and tuberin, play a key role in mammalian target of rapamycin (mTOR) pathway regulation. Decreased hamartin and tuberin expression results in hyperactive mTOR, which results in disinhibited cell growth and protein synthesis. Downstream consequences of mTOR pathway deregulation, including disorganization of axon tracks, aberrant myelination, and defects in synaptic plasticity, are believed to contribute to ASD symptoms.

Using a mouse model of TSC, we investigated ASD whole-brain macrocircuit abnormalities and potential drug-targets. We aimed to map the expression of the activity-dependent, immediate-early gene product c-fos via immunohistochemistry methods in wild-type and Tsc1 mutant mice to identify macrocircuit abnormalities in the brain. Specifically, we aimed to examine expression in the cerebellum, thalamus, prefrontal cortex, caudate nucleus, and nucleus accumbens. Concurrently, we treated TSC1 mutant mice with rapamycin with the aim of rescuing the identified macrocircuit abnormalities.

The tissue was prepared by anesthetizing mice with ketamine and transcardially perfusing with PBS followed by paraformaldehyde fixative. The brains were postfixed with paraformaldehyde, cryoprotected in sucrose, and stored at 4 degrees C. A cryostat microtome was used to cut 40 micrometer slices. Slices were stored in PBS at -20 degrees C. The c-fos immunostaining was performed by blocking the free floating 40 micrometer slices in buffer diluted normal goat serum for 1 hour and then incubating overnight at room temperature in primary antibody. Following rinse steps with buffer and PBS, sections were incubated in secondary antibody. The sections were mounted on plates and protected with coverslips.

No conclusions can yet be drawn from this ongoing study because immunostaining did not yield analyzable results. The problem was attributed to three potential sources: 1) the primary antibody used for the immunostaining procedure was degraded 2) the ketamine anesthesia used during perfusion blocked c-fos expression 3) the c-fos expression was too low to detect with fluorescence-labeled antibodies. To address the potential primary antibody problem a new primary antibody was ordered. This antibody will be used for future staining. To address the potential ketamine block of c-fos expression isofluorane was instead used for animal perfusions. Tissue prepared from the isofluorane anesthetized mice was stained with an avidin and biotinylated horseradish peroxidase complex procedure, a staining method designed for low expression proteins. No signal was detected for either tissue sample. We are continuing to work on identifying the confounding variables and optimizing the methods for this study.
The effect of decision fatigue on emergency providers

Keenan M. Mahan
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

Jeremiah D. Schuur, MD, MHS
Chief of Division of Health Policy, Department of Emergency Medicine
Brigham and Women’s Hospital

Emergency providers (EPs) frequently make decisions based on incomplete information over lengthy shifts with few breaks, increasing their risk of decision fatigue. Decision fatigue refers to the cognitive depletion and decision simplification and avoidance caused by repeated decision-making. The ability to sort out distracting information from meaningful information is an important part of our cognitive abilities, as much of what we perceive is not relevant to the tasks that demand our attention at any given moment. We hypothesize that over the course of a clinical shift, an EP’s executive functioning will decline.

This research has substantial implications for EP scheduling and emergency department (ED) organization. This study builds on analysis that correlates admission rates and test ordering with the time elapsed in a physician shift. Because providers have discretion about which patients they see, time in shift may not be a perfect indicator of cognitive load. By incorporating a direct measure of executive function, the Stroop effect test, our study allows for direct measurement of cognitive fatigue over the course of an EP shift.

This study will collect data from emergency providers using the Stroop effect test to measure executive function and a paper survey to measure overall ED business and if the providers have been taking breaks. The administration of the test and survey will take place in the ED at 3 points throughout a provider’s shift. We will also use electronic data to gather information about provider’s ordering and admissions statistics throughout their shift.

We will analyze the executive functioning data and ordering and admissions data independently for each physician. We will examine the relationships between executive function and time spent in shift, expecting to see a decline in function over the course of a shift. We will also examine how executive function relates to test ordering and patient admissions. We expect to see an increase in test ordering and patient admissions as time into shift increases and as executive function declines. Results are pending.

If decision fatigue is evident based on physicians’ declining executive function, a follow-up study would examine systems to combat decision fatigue. Studies show that maintaining an adequate blood glucose level, viewing nature scenes, experiencing positive mood, and having a short rest are all capable of relieving the effects of decision fatigue.
Cervical cancer is a preventable disease that has a devastating impact on women’s health around the world. The majority (~80%) of the global burden of disease due to cervical cancer occurs in low- and middle-income countries (LMICs) and it is the leading cause of cancer deaths among women. Screening through the use of Pap smears, has been effective in reducing the annual incidence of cervical cancer. In many LMICs, however, access to cervical cancer screening is limited, and women are at an increased risk of cancer-related mortality.

Our goal in this study was to understand the factors that influence cervical cancer screening among women in South Africa (SA). We specifically focused on evaluating the barriers to screening among HIV+ women. Studies have shown that HIV and Human Papillomavirus (HPV) work synergistically, leading to HIV+ women having higher rates of cervical-cancer related deaths compared to risk-matched HIV-negative women.

Using open-ended questions, we interviewed 30 women between the ages 30-65 years to assess their attitudes and beliefs about Pap smears and their knowledge of cervical cancer. The participants were from six different communities around Pietermaritzburg. 17 women were HIV+ and 13 women were HIV-negative. All interviews were audio taped, and transcribed. Three researchers (T.M, L.K, L.B) will independently read the transcripts and develop an initial codebook by consensus. All interviews will then be coded, using NVIVO software, and analyzed for themes.

Preliminary findings show that participants expressed high levels of interest in learning about the etiology of cervical cancer and the role of Pap smears. Most participants reported having at least one Pap test in their lifetime, but the majority did not obtain their results or return for follow up care. The role of patient autonomy and independent decision-making was a common theme across many participants. Participants, who were living with HIV, expressed a deeper understanding of cervical cancer screening than those who were HIV-negative.

While participants did not discuss structural barriers to cervical cancer screening, they generally felt that the burden of responsibility fell to them to learn about screening. All participants expressed fear of the procedure or expected pain as the major reason for delaying initiating the first Pap smear. The study shows that while Pap smears are offered at most clinics in Pietermaritzburg, women who access them still have little knowledge about their role in prevention, which is associated with decreased likelihood of repeat Pap tests.
Understanding the role of tumor-derived extracellular vesicles in breast cancer metastasis

Camille Mathey-Andrews
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

Judy Lieberman, MD PhD
Program in Cellular and Molecular Medicine, Boston Children’s Hospital, Harvard Medical School

Metastasis is responsible for the vast majority of cancer deaths. Initiation and progression of metastasis are multistep processes that involve a series of reciprocal interactions between the primary tumor and its microenvironment. Tumor-derived extracellular vesicles (EVs) and their nucleic acid, lipid, and protein contents have been shown to mediate crosstalk between cancer cells and the surrounding stroma, activating stromal cells towards a pro-metastatic phenotype. Cancer EVs also enter the circulation and are internalized by target cells in distant tissues, where they contribute to the establishment of the metastatic niche.

Previously, the Lieberman laboratory demonstrated that EVs are also transferred between cancer cells. In a seminal study, Le et al. found that EVs derived from highly metastatic breast cancer cells confer malignant traits to less metastatic cells, promoting lung colonization and metastasis formation by the recipient (target) cells. While this finding was consistent with reports that tumorigenic EVs are internalized by a variety of different cell types, the distribution of EV uptake by target cells in vivo remained, until now, unclear.

In the present study, I characterized target cells in the tumor microenvironment and lungs that took up EVs derived from triple-negative murine breast cancer tumors. I found that cancer EVs are internalized by 9% of macrophages, 7% of neutrophils, 34% of endothelial cells, and 70% of fibroblasts in the primary tumor stroma, and at low levels distally, in the lungs of tumor-bearing mice (less than 3% of all cells). Notably, I observed that EVs are taken up particularly avidly by fibroblasts, cells that have been implicated as critical drivers of breast cancer progression. My preliminary results suggest that EV internalization by fibroblasts is associated with the induction of genes known to promote the proliferation and invasion of nearby cancer cells. Future work will seek to elucidate whether EV uptake by host fibroblasts activates them towards a pro-metastatic phenotype, with the ultimate goal of identifying putative targets for novel breast cancer chemotherapies.
Correlation of 3D Neuroretinal Rim Thickness and Visual Fields in Glaucoma: A Broken Stick Model

Michael A. McClurkin
Harvard Medical School, William Bosworth Castle Society, Class of 2018
Ruthanne B. Simmons Scholars in Ophthalmology Fellowship

Teresa C. Chen, MD, FACS
Glaucoma Service
Massachusetts Eye and Ear Infirmary

**Purpose:** Glaucoma is the leading cause of irreversible blindness worldwide with characteristic changes to the retinal nerve fiber layer (RNFL) and optic nerve head (ONH). Clinical diagnosis of glaucoma has traditionally centered on optic nerve head evaluation, as the optic nerve head undergoes obvious structural changes prior to clinically detectable loss of visual function. As a result, glaucoma can progress insidiously with substantial structural damage occurring before clinical intervention. We performed a retrospective, cross sectional study to determine the “tipping point” at which visual field (VF) loss becomes associated with detectable three-dimensional (3D) neuroretinal rim thickness loss as measured by optical coherence tomography (OCT). We hypothesize that there will be clinically detectable loss of 3D neuroretinal rim thickness before VF loss.

**Methods:** 58 healthy and 104 glaucoma subjects (one eye per subject) were recruited from an academic institution. All patients had VF examinations (Swedish Interactive Threshold Algorithm 24-2 test of the Humphrey visual field analyzer 750i; Carl Zeiss Meditec, Dublin, CA) and spectral domain optical coherence tomography 3D neuroretinal rim scans (Spectralis, Heidelberg Engineering, Heidelberg, Germany). Comparison of 3D neuroretinal rim thickness values with VF threshold values showed a plateau of VF threshold values at high 3D neuroretinal rim thickness values and then a sharp decrease at lower 3D neuroretinal rim thickness values. A broken stick statistical analysis was utilized to estimate the tipping point at which 3D neuroretinal rim thickness values are associated with VF defects. The slope was computed for data above and below the tipping point.

**Results:** The average age of 162 patients was 63.08 years; 54.3% were females; 65.4% were white. The mean 3D neuroretinal rim thickness value that was associated with initial VF loss was 0.1923 mm. The superior 3D neuroretinal rim thickness value that was associated with initial corresponding inferior VF loss was 0.2172 mm. The inferior 3D neuroretinal rim thickness value that was associated with initial corresponding superior VF loss was 0.1975 mm. The differences between all the slopes above and below the aforementioned tipping points were statistically significant (p<0.001).

**Conclusions:** In open-angle glaucoma, substantial 3D neuroretinal rim structural loss and optic nerve damage appears to be necessary before functional visual field vision loss becomes clinically detectable.
Efficacy of Icon Application on White Spots of Various Etiologies - A Pilot Study

Kalie McCulloch
Harvard School of Dental Medicine, William Bosworth Castle Society, Class of 2018

Maria Grazia, DDS, PhD; Angel Turi, RDH
Oral Pathology Department,
University of Milan; Intini Dental Office

White spots are a concerning aesthetic issue within the field of dentistry and arise for several different reasons. Etiologies of these lesions may be partitioned into two broad categories: developmental or acquired. Developmental lesions may arise from hypoplasia, hypomineralization, and hypocalcification whereas acquired lesions are a consequence of poor dental hygiene practices while undergoing orthodontic treatment.

High coefficient resin infiltration (Icon®, DMG Inc., Germany) is a new therapeutic option that may replace more invasive procedures. In this pilot study, the efficacy of this resin with various lesions from different etiologies was tested. It was hypothesized that by affecting only the more superficial layers of the enamel, compared to white spots with developmental etiologies, white spots with acquired etiologies respond better to the Icon® treatment option.

Photos were obtained pre and post treatment using standardized distance, lighting, exposure, and timing. By means of NIH Image J, the difference in gray scale values pre and post Icon Treatment was quantified. After uniformly assigning the photos to an 8-bit scale, the NIH Image J threshold feature was used to identify a range of gray scale values that unequivocally identified the white lesion in untreated lesions and then compared the measured values in photos obtained after treatments. Internal controls consisted of the same measurements performed on untreated areas of the same teeth. To ensure consistency, a manual method was also utilized to cross reference results.

A total of four different patients with several white spots were treated. Three patients were affected by development lesions while the remaining patient acquired white spot lesions after orthodontic treatment. Developmental lesions in two out of three patients responded well to treatment as well as the acquired lesion as per NIH Image J measurement and patient satisfaction. However, in the remaining patient, there were observed changes in terms of gray scale values but patient was not satisfied and no clinically appreciable changes were seen.

Based on these preliminary results it is suggested that the efficacy of Icon treatment across different lesion etiologies varies. A more comprehensive study that includes a statistically useful number of samples per etiological group will be required to confirm these impressions.
A Refillable Anti-Thrombogenic Surface Treatment for Vascular Devices

Stephanie L. McNamara
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

David J. Mooney, PhD
Harvard University School of Engineering and Applied Science
Wyss Institute for Biologically Inspired Engineering

Thrombosis is a frequent complication associated with medical devices such as catheters, stents, and mechanical heart valves. Vascular grafts or catheters placed in direct contact with the blood frequently induce activation of the coagulation cascade leading to occlusion of the device or embolization of dislodged clot. Bioengineering efforts aimed at addressing graft-related thrombosis in small vessel grafts and catheters have focused on surface treatments using anti-thrombogenic molecules. However, this approach is limited by its single use nature. Once degraded, there is no way to replenish the anti-thrombogenic surface without replacing the graft or catheter line.

In this study, we applied DNA toehold exchange methods to develop a refillable, anti-thrombogenic surface treatment for catheters and vascular grafts. This system involves a surface-bound DNA strand and two complementary DNA strands that can bind to the surface-bound strand and each carry a thrombin-binding DNA aptamer (TBA). These TBA-carrying strands can displace one another via DNA toehold exchange.

We hypothesized that the TBA-carrying strand would home to the graft and bind to the surface-bound DNA strand, allowing for the expression of TBA on the implanted device. Once bound to thrombin, the TBA could be replaced by introducing a second TBA-carrying strand that binds to a unique toehold region on the surface-bound DNA strand and displaces the currently bound TBA-carrying strand.

We used thrombin-mediated fibrin gelation as a measure of thrombin activity to assess the ability of the DNA-bound TBA to inhibit thrombin activity on the surface of 3 French catheters. Treatment of a catheter surface area of 25 mm² with the TBA-carrying DNA system resulted in a 17% reduction in fibrin gelation compared to the non-treated control.

To prove that DNA toehold exchange could be used to maintain this anti-thrombogenic surface, we used a 5’ to 3’ exonuclease to selectively digest the surface bound aptamer and demonstrated the ability to refresh the surface with new TBA. Preliminary tests of multiple replacement have shown that the exposure of a TBA-bound surface that was treated with exonuclease to a TBA refill restores thrombin inhibition. This was indicated by a 54.3% reduction in fibrin gelation compared to the non-TBA treated control, and a 52.9% reduction in gelation compared to an exonuclease-treated TBA-bound surface (p < 0.01).

These data indicate that this system can be applied to create a refillable drug-bound surface that can be used to maintain anti-clotting properties and prevent the need for vascular graft replacement.
Genomic predictors of response to CTLA4 blockade in metastatic melanoma

Diana Miao
Harvard Medical School, Irving M. London Society, Class of 2018
Alexandra J. Milliotis Fellowship in Pediatric Oncology

Eliezer Van Allen, MD
Department of Medical Oncology, Dana Farber Cancer Institute

Melanoma is one of the most common adult cancers, with more than 70 thousand estimated new cases in 2015 resulting in almost 10 thousand deaths. An absence of targeted chemotherapies for melanoma until the early 2010s has led to poor prognoses for late-stage disease, with 5-year survival rates below 20%. However, recently developed immunotherapies such as ipilimumab, a monoclonal antibody that blocks the T-cell inhibitory receptor cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), have led to significant gains in survival in large clinical trials. While overall single-agent response rates are low, a sustained clinical benefit is consistently observed in ~20% of patients. However, clinical predictors of response remain unknown. Elucidating such response effectors may impact patient selection, clinical trial design, and therapeutic development of this new class of cancer drugs.

Preclinical and clinical studies have suggested that tumor-specific peptides generated by somatic nonsynonymous mutations that bind to patient HLA class I molecules (neoantigens), NRAS mutation status, or RNA-based signatures of the tumor microenvironment may explain response to cancer immunotherapy. However, an integrated analysis incorporating whole exome and whole transcriptome sequencing of pre-treatment tumors from a large (>100) cohort of patients who received CTLA-4 inhibitors has yet to be done. We hypothesize that tumor-specific genetic alterations, immune-related factors in the tumor microenvironment, or expression of tumor neoantigens may influence clinical benefit from immune checkpoint blockade.

In this study of 110 patients with late-stage melanoma treated with ipilimumab, we found that overall mutational load and neoantigen load were significantly correlated with clinical benefit (p = 0.0076 and p = 0.027, respectively), as were expression of GZMA and PRF1, two markers of cytolytic activity in the tumor microenvironment (p = 0.042), and expression of CTLA-4 itself (p = 0.033). Neoantigens were unique to a given patient in the vast majority of cases, and only 28 neoantigens (<0.04%) were found in more than 1 patient who achieved clinical benefit from ipilimumab but in none who experienced minimal clinical benefit. Thus, the sample size necessary to discover specific or recurrent neoantigens that mediate response to immunotherapy may be orders of magnitude higher than that currently available. Both RNA- and DNA-level information have predictive value for response to ipilimumab, and additional studies of clinical response to immune checkpoint inhibitors may benefit from integrating exome and transcriptome data to inform the relative contributions of tumor immunogenicity and host immune infiltration in determining clinical benefit.
The Impact of an Option B+ Prevention of Mother to Child Transmission Program on HIV+ Mothers in Mbarara, Uganda

Kathleen Miller
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Mark Siedner, MD, MPH
Massachusetts General Hospital

In 2013, the WHO issued updated guidelines for prevention of mother to child transmission (PMTCT) of HIV, recommending initiation of a full ART treatment regimen (termed PMTCT Option B/B+) instead of the previously recommended use of 1-2 drugs for women with higher CD4 counts (termed PMTCT Option A). Although early data are positive, few studies have investigated outcomes for pregnant women related to the switch to Option B+ on a clinic-wide scale.

We conducted a retrospective analysis of data collected at government-operated HIV clinic in Mbarara, Uganda before and after the policy change from Option A to Option B+. We hypothesized that the switch from Option A to Option B+ has improved the speed at initiating ART therapy, improved clinical outcomes, and increased retention in care.

We limited our analysis to women who were not on ART before pregnancy and whose pregnancy CD4 counts were over 350. Our primary exposure of interest was the enrollment period, based on first pregnancy date. Our primary outcomes of interest were a) CD4 counts and change in CD4 one year post pregnancy, b) time to ART initiation, and c) retention in care one year after pregnancy. We fit bivariable and multivariable (adjusted for age, time to clinic, and marital status) logistic regression models to estimate relationships between the observation period (A vs B+) and each of the outcomes of interest.

A total of 1048 women were included in the analysis, 526 (49.8%) in the Option A period and 522 (50.2%) in the Option B period. There were no significant differences between the groups in age, marital status, or distance from the clinic. We found that women in the Option B+ period did start ART treatment significantly earlier (1084 days vs 29 days, P-value < .0001) and did have increased therapeutic efficacy based on CD4 change 1 year after pregnancy (+4 vs +138.5, P-value < .0001). However, there was no significant difference in the proportion of women retained in care for women between the two periods (69.4% vs 71.7%, P-value .423). These relationships persisted in multivariable regression models.

Although there may be significant health benefits to an Option B+ PMTCT program, these benefits may not include increased retention in care. Limitations included use of a retrospective analysis of a non-randomly allocated intervention, which can be challenged by both unmeasured and residual confounding; and lack of clinical outcomes (e.g. death, hospitalizations).
Ovarian cancer kills more women than any other cancer of the female reproductive system. According to the American Cancer Society about 22,000 women will be affected and 15,000 women will die from ovarian cancer in 2015; limited effective treatment options keep the five year mortality rate at just under 70%.

Mullerian Inhibiting Substance (MIS) is a hormone which is expressed by the fetal testes and causes embryonic regression of the Mullerian ducts, which would otherwise develop into the uterus, cervix, and upper third of the vagina, in the male. MIS has been shown to inhibit the growth of epithelial ovarian cancer cell lines \textit{in vitro} and \textit{in vivo}, and thus has been proposed as a potential anti-cancer agent. Our objective is to elucidate the mechanism of action by identifying genes regulated by MIS and identify biomarkers predictive of response.

Primary human ovarian cancer cells, derived from 4 patient ascites, were treated \textit{in-vitro} with recombinant MIS (5ug/ml) or vehicle control. Gene expression analysis was performed using an Illumina MiSeq RNA sequencer, generating 15 million reads per sample. Pathways were identified which had significant enrichment of genes modulated more than 2 fold (log2) by MIS treatment. Modulation of expression of these genes by MIS was validated \textit{in-vivo} by analyzing gene expression by qPCR in tumors from patient-derived xenograft models treated with MIS gene therapy. Ascites cells from patients (1-5E6) were implanted subcutaneously into groups of 10 Nu/Nu or NOD/SCID Gama mice. Half of the mice were injected intraperitonealy with an adeno associated virus (AAV9) control, and the other half with an AAV9 optimized for MIS delivery. Total cellular RNA was then extracted from the tumors at endpoint.

Analysis of RNA-seq identified roughly 1800 genes distributed across the four patients that were either up or down regulated at least four times higher or lower in the MIS treated mice. 178 genes were consistently regulated by MIS in more than one patient cell line. A panel of 11 genes representing major nodes of pathways enriched for MIS-respose were validated by qPCR. To date, two genes, inhibin A (P=0.04) and Sox10 (p=0.01) have been shown to have statistically significant down regulation associated with MIS treatment.

Continued investigation of new genes and validation of current genes will continue as this project moves into the fall. Validated candidates will then be evaluated for their ability to predict patient response in patient-derived xenograft models.
Assessing oral health knowledge and behaviors of residents of the province of Loreto, Peru

Kellie L. Moore
Harvard School of Dental Medicine, Oliver Wendell Holmes Society, Class of 2018

Adam Frange, BA
Leder Human Biology LHB – Division of Medical Sciences
Harvard Medical School

Tooth decay is largely preventable; however, dental caries remains the most common chronic non-communicable disease in the world. Risk factors contributing to dental caries include high sugar consumption, poor nutrition, lack of fluoride, poor dental hygiene and tobacco use, among other factors. Worldwide, the prevalence of dental caries affects up to 90% of children and nearly 100% of adults, with the highest prevalence of disease concentrated in developing countries. Dental caries cause severe pain and affect daily activities including eating, speaking, and social dynamics.

In this study, our region of interest was the province of Loreto, Peru. We sought to better define the prevalence of dental caries in the area, with a focus on the element of individual behavior and its association with oral health outcomes. We hypothesized that many residents of the region would demonstrate limited oral health knowledge, and that a correlation would exist between limited oral health knowledge, poor oral health behaviors, and increased dental caries levels.

To test these hypotheses, adult residents of Loreto, Peru, were given oral surveys to assess their knowledge about oral health and their oral health behaviors. Participants were given oral examinations to determine their decayed, missing, and filled teeth (DMFT) index as a cross-sectional measurement of dental caries prevalence.

117 consenting adult residents from the cities of Iquitos and Nauta, and the smaller communities of Amazonas, Payarote, San Francisco and Santa Cruz, were administered a 10-15 minute oral survey with questions concerning their oral health knowledge, dental hygiene behaviors and dental visit history. They were then given a brief oral examination to determine their DMFT index.
Food Insecurity and Cardiovascular Health in Pregnant Women: Results from the Food for Families Program

Mary E. Morales
Harvard Medical School, Francis Weld Peabody Society, Class of 2018

Seth A. Berkowitz MD, MPH
Department of Internal Medicine, Massachusetts General Hospital

In the US, cardiometabolic diseases such as heart disease, diabetes, and hypertension are leading causes of morbidity and mortality. Food insecurity, the uncertain ability to acquire nutritious food in a socially acceptable manner, is associated with cardiometabolic disease in the general population, and with poor birth outcomes in pregnant women. However, it is not known whether programs to combat food insecurity in pregnant women are associated with better cardiovascular health.

The Foods for Families (FFF) program strives to identify food insecure patients and connect them with resources, such as the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) and food pantries, to improve access to healthy foods. We investigated characteristics of participants and estimated its impact on blood pressure and glucose in a population of pregnant women.

We conducted a retrospective analysis of all women who visited the obstetrics clinic at the MGH Chelsea Healthcare Center between 2013 and 2015. We hypothesized that participation in FFF would be associated with better blood pressure and glucose levels among food insecure patients. To reduce bias from differential entry into FFF, we used a propensity score matched design to evaluate trends in systolic blood pressure (SBP) and glucose among FFF participants and non-FFF participants. Propensity scores were constructed using demographic, clinical, and neighborhood characteristics.

Eleven percent of women who visited the obstetrics clinic were identified by FFF. Among FFF participants, 71% had annual incomes below the federal poverty level, 46% reported housing insecurity, and 87% were enrolled in WIC. Compared with patients not identified as food insecure, food insecure participants were more likely to be unmarried (63% vs. 45%, p=0.01) and speak Spanish (77% vs. 34%, p=0.001). In propensity score matched analyses, there was no difference in SBP between FFF participants and non-participants at baseline (113.5 vs. 114 mm/Hg, p=0.79). However, FFF non-participants saw an increase in SBP (0.1 mm/Hg per week of pregnancy) during pregnancy, while FFF participants’ blood pressures were stable (p=0.0006). We observed no differences in glucose trends between groups (p=0.40).

FFF participation was associated with better blood pressure control in pregnant women, but no differences in glucose level. While propensity scores accounted for measured confounding, residual confounding by unmeasured factors may remain. Future studies incorporating randomized program entry would provide stronger evidence of effectiveness. Further, subsequent studies should address which program elements can be efficacious, and if program modifications or additions could lead to improved glucose control.
Predictors of Disease Progression during Surveillance of Patients with Asymptomatic Carotid Artery Stenosis

Ramya C. Mosarla
Harvard Medical School, Francis Weld Peabody Society, Class of 2018

Mark F. Conrad, M.D.
Department of Vascular Surgery
Massachusetts General Hospital

Direct and indirect costs combined, ischemic stroke is estimated to exceed 2.2 trillion dollars in healthcare expenditure from 2005 to 2050 in the United States. Currently, it is the third leading cause of death. Monetary and human costs make optimal management of at-risk patients a top priority. Of all ischemic strokes occurring in the US, 10-20% are estimated to be due to high-grade (>70%) asymptomatic ipsilateral carotid stenosis.

Both the degree of carotid stenosis and progressing stenosis have been reported as factors that increase the risk of cerebral ischemic events. These parameters have been used in both assessing an asymptomatic patient’s risk of developing neurological sequelae and guiding treatment. Patients with moderate stenosis (50-69%) are typically medically managed, while those with severe stenosis (>70%) are recommended for carotid endarterectomy if they are eligible for surgical intervention.

Two hundred-sixteen patients who presented with moderate stenosis from 2008-2009 were monitored through their medical records for the endpoints of plaque progression, appearance of ipsilateral neurological symptoms, and death. At present, the guidelines for optimal medical therapy (OMT) for these patients includes treatment with aspirin, statins, and the maintenance of an LDL level < 100 mg/dL. Group analysis of this cohort will seek to determine if there were differences in OMT between the patients who experienced disease progression and those who remained progression free. Additional patient characteristics such as medications and comorbidities will also be compared to evaluate if there are significant differences between patients who demonstrate disease progression and those who remain progression free. Improved understanding of protective and progression promoting variables will provide insight into how to best manage patients with asymptomatic carotid stenosis.
Global Benchmarking of Risk-Adjusted Surgical Outcomes: A Pilot

Jessica L. Mueller
Harvard Medical School, Walter B. Cannon Society, Class of 2018

Richard T. Spence, MD, MPH
Codman Institute for Clinical Effectiveness in Surgery
Massachusetts General Hospital

It is difficult to develop strategies to improve global surgery care when the influence of interventions is currently almost immeasurable with the existing tools in most resource-limited environments. This could change if there was global consensus on not only the standardization of a minimal collected dataset but also the analysis thereof. With the advent of freely available risk calculators, we propose a means to calculate population based O/E (Observed/Expected) ratios, making global surgical benchmarking a possibility.

In a prospective cohort study, the first 40 consecutive operations of major general and vascular surgery cases on adults >13 years during an 8-day cycle for 12 cycles during a 3 month period (April 1st-June 30th 2014) at a teaching hospital in South Africa were included. Data variables required by the ACS risk calculator were prospectively collected. Risk-adjusted outcomes benchmarked against the ACS-NSQIP consortium were generated by calculating O/E ratios with 95% CI’s for 10 outcome measures of interest. Expected (E) measures were calculated by summing the individual risks for each adverse event predicted by the ACS-NSQIP calculator. Logistic regression was employed to validate the predictors used by the risk calculator to predict the risk of mortality, morbidity, length of stay (LOS) >30 days, and unplanned reoperation at our hospital.

373 major general and vascular surgery procedures met the inclusion criteria. The operative cohort varied significantly compared to the ACS-NSQIP consortium for every confounder variable included in the calculator. The risk-adjusted O/E ratios were significant for any complication O/E 1.91 (95% CI 1.57 – 2.31), surgical site infections O/E 4.67 (3.64 – 5.89), renal failure O/E 4.5 (95% CI 2.06 – 8.54), death O/E 3.43 (95%CI 2.19 – 5.11), and LOS O/E 2.97 (95% CI 2.86 – 3.07).

Utilizing the ACS-NSQIP risk calculator to benchmark surgical outcomes allows institutions to target particular areas for intervention. In global surgery, the need to improve both coverage and quality of surgical care is paramount. As our data suggests, the universal risk-calculator developed by the ACS may provide such a solution. Given its accurate predictive ability and use of readily available variables, we propose that this calculator be used to guide collection of a minimal dataset and as a tool for calculating risk-adjusted surgical outcomes and global benchmarking even in the most resource-limited settings.
Water insecurity and emotional distress: population-based, mixed methods study in rural Uganda

Rumbidzai Mushavi
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Alexander Tsai, MD, PhD
Division of Global Psychiatry, Psychiatry
Massachusetts General Hospital

Lack of access to water is an important public health issue. Most work in this area has focused on the health impacts of inadequate access to water or insufficiency of water. Little work has focused on the mental health impacts of water insecurity, which is a broader construct that incorporates social dimensions that have heretofore been overlooked.

I conducted a population-based, mixed-methods study among adult women living in Nyakabare Parish, Mbarara District, Uganda. Of 358 women in the population sampling frame, 327 were successfully interviewed (response rate, 91%). The median age was 31 years (IQR, 27-38), and 165 (50%) had completed primary school. Water insecurity was measured with a novel 8-item Household Water Insecurity Access Scale, which had a median value of 9 (IQR, 4-15), indicating a moderate to severe degree of water insecurity in the population. Based on the 15-item Hopkins Symptom Checklist for Depression, 136 women (42%) had significant emotional distress / probable depression.

In multivariable linear regression, there was a statistically significant association between depression and water insecurity (b=0.013; 95% CI, 0.005-0.02) after adjusting for age, education, marital status, household wealth, and self-reported overall health. Expressed differently, an increase in water insecurity from the 25th percentile to the 75th percentile of intensity was associated with an increase in probable depression from 35% to 48%. I selected 28 women for in-depth, qualitative interviews. At the time of this writing, 13 qualitative interviews have been completed and the analysis is not yet complete. Emotional distress resulting from water insecurity has emerged as a prominent theme in the qualitative interviews. As one 28 year-old mother of 4 stated, “I found that there was no one to help me. If only I had someone to bring the water...but I found myself here alone with no help......Aaaah.....you know you start thinking a lot and even Satan can tempt you and you start thinking, ‘Why did I even get married?’ So that day, when you find yourself sick and when you have no one to help you fetch water...that day makes you think a lot.”

The association between water insecurity and emotional distress is statistically significant and substantive in magnitude. Data from the qualitative interviews corroborate these findings and provide key narratives that reveal the mechanisms through which people’s lived experiences may lead to emotional distress.
The Impact of Intraoperative Adverse Events on Hospital Readmission

Anirudh R. Nandan
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Haytham Kaafarani, MD, MPH
Division of Trauma, Department of Surgery
Massachusetts General Hospital

The Centers for Medicare and Medicaid Services (CMS) routinely use 30-day patient readmission rate as a hospital benchmarking quality metric. We sought to study the independent impact of major intraoperative adverse events (iAEs) on 30-day readmissions in abdominal surgery.

The 2007-2012 institutional American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) and administrative databases for abdominal surgeries were matched and screened for iAEs using the ICD-9-CM-based Patient Safety Indicator “Accidental Puncture/Laceration”. Flagged charts were reviewed to confirm the presence of iAEs, as defined by the Institute of Medicine. Major iAEs were further defined as Class 3 or above, as per the validated Kaafarani iAE Classification System. The institutional Research Patient Data Registry (RPDR) was queried to identify postoperative readmissions that occurred within 30 days of discharge. Univariate and multivariable models were constructed to analyze the independent impact of major iAEs on 30-day readmission, controlling for preoperative and intraoperative variables such as comorbidities, American Society of Anesthesiologists (ASA) class, procedure complexity, and procedure type. Reasons for readmission (from admitting ICD-9 codes) were grouped into categories using the Clinical Classification Software provided by the Agency for Healthcare Research and Quality (AHRQ).

Of 9288 surgical procedures, 183 had documented iAEs, 73 of which were major iAEs. The overall rate of readmission was 10%. In univariate analyses, procedures with major iAEs had a higher readmission rate when compared to procedures with no iAEs [25% vs. 10%, P<0.001]. In multivariable analyses, major iAEs were independently associated with more than two-fold increase in the rate of readmission [OR=2.22, 95%CI: 1.25-3.94, P=0.007]. Of all readmissions after major iAEs, 67% were caused by “complications of surgical procedures or medical care” as defined by AHRQ.

Major iAEs are independently associated with an increased rate of 30-day readmission. Preventing or mitigating the effects of iAEs during surgery can potentially decrease the rates of hospital 30-day readmission.
Determinants of Unrepaired Third and Fourth Degree Perineal Lacerations Contributing to Obstetric Fistula Burden: An Assessment of Senior Midwife Trainers in Western Kenya

Kelsey Natsuhara
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Thomas F. Burke, MD, FACEP, FRSM
Division of Global Health and Human Rights
Massachusetts General Hospital, Boston, MA

Obstetric Fistula (OF) is a complication of childbirth that results in fecal and/or urinary incontinence due to breakdown of the tissues normally separating the vagina from the bladder and/or rectum. OF affects approximately two million women globally, causing significant physical and psychological burden. OF has been almost eliminated in high-income countries, but continues to burden women in low- and middle-income countries. Furthermore, there is confusion surrounding the diagnosis of OF versus unrepaird third- and fourth-degree perineal lacerations in East Africa. In a recent study, we found that 32% of women undergoing OF repair in Western Kenya actually suffered from unrepaird third- and fourth-degree perineal lacerations. Third- and fourth-degree perineal lacerations are characterized by tears from the vagina into and through the anal sphincter, respectively, and result in symptoms indistinguishable from OF. However, these injuries require significantly fewer resources and less time to repair than OF and can be identified at the time of delivery and fixed immediately post-partum.

Therefore, if nearly one in three women suffering from the symptoms of OF have unrepaired third- and fourth-degree perineal lacerations, one might imagine that it is possible to alleviate a considerable portion of the global fistula burden through the development and deployment of improved education and training for skilled birth attendants in the immediate postpartum identification and repair of these injuries. We hypothesized that the ability to accurately diagnose, repair, and/or refer acute and chronic third- and fourth-degree perineal lacerations in Western Kenya was poor and sought to test this hypothesis.

We assessed the ability of twenty-two senior midwife trainers in Siaya County to accurately identify and classify obstetric lacerations, identify anatomical structures of the perineum, and repair obstetrical lacerations using an interactive pictorial- and model-based tool. Referral pathways, follow-up mechanisms, and barriers to evaluating obstetrical lacerations were also assessed. The senior midwives all scored extremely poorly (mean±SD, 9.55%±6.0% correct answers) in their ability to recognize and/or repair perineal lacerations.

We conclude that the current ability of senior midwife trainers in this large county in Western Kenya to diagnose and refer third- and fourth-degree perineal lacerations is poor, highlighting the need to develop and deploy a best-evidence training module to improve the treatment and outcomes of obstetric perineal lacerations.
The impact of body habitus on the outcomes after aneurysmal subarachnoid hemorrhage: A nationwide analysis

Michael O. Nguyen
Harvard Medical School, Francis Weld Peabody Society, Class of 2018

Rose Du, MD, PhD
Department of Neurological Surgery
Brigham and Women’s Hospital

Object. Few studies have evaluated the impact of obesity on the outcomes of patients with aneurysmal subarachnoid hemorrhage (SAH). This is the first nationwide analysis to examine the effect of body habitus on in-hospital mortality, complications, length of stay, and discharge disposition after aneurysmal SAH.

Methods. Two national data sets were analyzed, consisting of 17179 patients from 2002 and 2010 in the Nationwide Inpatient Sample (NIS) database and 321 patients from 2007 and 2013 in the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database. Data collected included patient demographic features (e.g. age, sex, and BMI) and severity of SAH at admission (e.g. ventilation status, ASA class, and Hunt-Hess grade). For each data set, outcome after aneurysmal SAH was assessed for by in-hospital mortality, total complications, readmission to the operating room, length of stay, and discharge disposition. Body mass index (BMI) was evaluated for its impact on these outcomes using multivariate logistic regression.

Results. In the NIS cohort, 16377 patients were nonobese (BMI < 30 kg/m²), 530 patients were obese (BMI >= 30 kg/m² but <= 40 kg/m²), and 272 patients were morbidly obese (BMI > 40 kg/m²). In the multivariate analysis, BMI was not a significant predictor of in-hospital mortality, complications, readmission to the operating room, or length of stay. There was a significant association between BMI > 40 kg/m² and a nonroutine discharge (odds ratio [OR]: 1.49, 95% confidence interval [CI]: 1.13-1.97, p = 0.005). In a subanalysis of NIS patients who underwent endovascular coil embolization, obesity and morbid obesity were significant predictors of not returning to the operating room (OR: 0.66, 95% CI: 0.44-0.99, p = 0.043) and having a nonroutine discharge (OR: 1.53, 95% CI: 1.04-2.26, p = 0.031), respectively. Among the NSQIP patients, 211 were nonobese, 86 were obese, and 24 were morbidly obese. In the multivariate analysis, there was not a significant association between BMI and in-hospital mortality, complications, readmission to the operating room, length of stay, or discharge disposition.

Conclusions. The results of the study suggest that BMI is not an independent predictor of in-hospital mortality, complications, or length of stay. Morbid obesity, however, is associated with a higher incidence of nonroutine discharge. Furthermore, in patients who underwent endovascular coil embolization, obesity was associated with a lower likelihood of readmission to the operating room while morbid obesity was linked to an increased probability of a nonroutine discharge.
An evaluation of attitudes among members of the Navajo Nation community
towards the availability and affordability of healthy and traditional Navajo foods in
local stores

Laura Nicholson
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Sonya Shin, MD, MPH
Harvard Medical School
Brigham and Women’s Hospital, Division of Global Health Equity
Partners in Health, Boston, MA
Community Outreach and Patient Empowerment, Gallup, NM

American Indian (AI) communities experience a large number of health
challenges, including higher rates of chronic disease compared with other populations in
the U.S. Although many factors underlie poor health outcomes, limited access to healthy
food has been identified as one of the key drivers of health disparities in rural AI
communities. Small stores on the Navajo reservation often have limited healthy options,
sold at higher prices compared to similar stores off the reservation. We sought to
understand the perspective of local customers on the availability and pricing of healthy
foods and traditional Navajo foods in local small stores.

We held three focus groups in the Navajo Nation chapters of Ramah, Blue Gap
and Sheep Springs. A total of 27 community members who reported shopping at their
local small store participated in the groups. Focus groups were conducted in English.
Interviews were transcribed and coded according to themes, which were analyzed using
standard qualitative techniques.

Preliminary findings show that community members encounter barriers when
shopping for healthy food locally. These barriers include cost, value and quality,
freshness, limited variety, and low availability of healthy foods. There are mixed
opinions on whether enough frozen foods are available in local stores and whether more
frozen produce should be offered. Many participants feel that traditional Navajo food
options in local stores are limited. There is interest in increasing offerings of Navajo
foods and fresh produce, and concerns about higher costs of fresh produce.

The needs and concerns of community members must be taken into
consideration to provide more healthy, affordable food for their communities. Linking
retailers to local producers – including traditional Navajo foods – and finding ways to
reduce costs to the consumer could be effective strategies to increase access to affordable,
local healthy food. A better understanding of consumer perspectives will inform
strategies to partner with community members and local retailers in a Healthy Navajo
Stores Initiative.
Adequacy of Prenatal Care and Sex Ratios in Humans

Deyang Nyandak
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

James Edward Zuckerman, MD
Assistant Professor of Obstetrics, Gynecology and Reproductive Biology
Brigham and Women’s Hospital

The human sex ratio has been of interest to many evolutionary biologists, including Charles Darwin. However, Darwin appreciated the complexity of the allocation of sex ratios by stating he would leave the issue for the future generation to solve. In human populations, the average secondary sex ratio (sex ratio at birth) is 1.03:1 (male:female). However, a range from 1.06:1 (Asian newborns) to 1.028:1 (American Indian newborns) is seen. Higher male sex ratios were found in a poverty stricken Venezuelan population for cohabitating and married couples, while the male sex ratio decreased when single mothers were caring for the children. In addition, a meta-analysis noted the decrease in male sex ratio following the decline in the annual consumption of goods and services by individual households in Sweden.

In this study, we obtained data from the Massachusetts Department of Public Health website and MASSCHIP Community Health Information Profile, including the adequacy of prenatal care, and sex ratio at birth. The adequacy of prenatal care was categorized according to the Kessner Index, which refers to the number of prenatal visits according to how far along the mother is in her pregnancy. We used data from 1989 to 2013 and will use R to analyze the relationship of adequacy of prenatal care and sex ratio at birth. A simple ratio calculation and observation, however, suggests that there is no relationship between the two. Births were mainly male dominant across all the categories of care (adequate, intermediate, inadequate and no care). A more extensive data analysis with R may show some subtle differences.

Given the lack of differences in sex ratio between the categories of care, we can speculate that the trajectory of sex ratio changes is over by the time prenatal care starts. My mentor, Dr. James Zuckerman, and colleagues investigated the trajectory of human sex ratio at conception (primary sex ratio) and during the course of pregnancy. They found that the primary sex ratio is 1:1 (male:female) and dynamics of sex ratio occurs within the first 15 weeks of pregnancy. Therefore, it is possible that since sex ratio adjustment occurs very early on during the pregnancy and the mother’s access to facilities such as good nutrition and social support during later stages of pregnancy may not have an impact on the sex ratio at birth.
Systematic Review of Oral Ulceration with Bone Sequestration

Benjamin L. Palla
Harvard School of Dental Medicine, William Bosworth Castle Society, Class of 2018

Sven Otto, MD, DDS, FEBOMFS
Department of Oral and Maxillofacial Surgery
Ludwig-Maximilians-Universität, Munich, Germany

This article represents the first systematic review entirely dedicated toward a disease called oral ulceration with bone sequestration (OUBS). Authors and practitioners have used OUBS variably to characterize oral ulceration and bone sequestration occurring without an etiologic cause. We performed this review in order to further define and outline this concept. A secondary interest was to recognize the prevalence and importance of OUBS in relation to other oral disorders accompanied by ulceration and bone exposure.

The systematic review was registered with PROSPERO (registration number CRD42015024294) and performed in cooperation with Harvard’s Countway Library. Searches were built using MeSH terms and proximity operators from previously mentioned OUBS descriptions. Database searches were performed through EMBASE, Medline, and PubMed, followed by a handsearch of bibliographies for relevant articles. Articles were assessed against eligibility and inclusion criteria centering on bone exposure without known etiologic cause. We sought to gather information on patient age, sex, anatomical location, clinical presentation, and comorbidities. PRISMA guidelines were followed.

The searches identified 766 records total. Despite considerable inspection, we found only 8 articles qualifying for our review. In the 8 articles, there were a total of 24 patients fulfilling the criteria of OUBS. Although some abstracts mentioned an idiopathic nature of ulceration, most authors presented clinical cases that displayed a probable etiologic cause to ulceration and sequestration. The mean age of these patients was 43.21± 11.94 years. The male to female ratio was 3:1. The predominant area of occurrence was the mandible (n= 23, 95.8%).

The current findings of this systematic review demonstrate that the OUBS concept cannot be regarded as one distinct entity, but rather it incorporates multiple, ulcerative disorders occurring in various locations, and due to a variety of both local and systemic effects. This paper identifies multiple etiologic causes of ulceration, predisposing factors for certain anatomical areas and abnormalities, and discusses the link between ulceration and subsequent insult resulting in bone sequestration.

The representation of OUBS in the literature remains scarce. More clinical data must be generated and gathered following guidelines provided in this paper. This will allow for a better determination of the true incidence and importance of this disease. Despite rare occurrences of conditions characterizing OUBS, the recent dialogue pertaining to this topic in the scientific community necessitates a call for more data to come forth and benefit patients suffering from challenging ulcerative disorders.
Assessing the implementation of a program to improve serious illness conversations in a high-risk care management program in the primary care setting

Marissa C. Palmor
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Joshua R. Lakin, MD
Palliative Care, Dana-Farber Cancer Institute & Ariadne Labs

For patients living with serious illness, conversations about goals of care have been shown to increase concordance between patients’ wishes and the care they receive, improve patient quality of life, and reduce caregiver distress. However, few clinical settings use formal protocols for prompting and conducting these conversations. The Serious Illness Care Program was developed to provide a structured approach for training, triggering, conducting, and documenting conversations about goals and wishes in serious illness.

We sought to assess the Program’s effect on frequency, timing, and quality of conversations for patients in a high-risk care management program in the primary care setting. In this prospective cohort quality improvement study, patients were selected using the question, “would you be surprised if this patient died in the next two years?” Intervention clinics received a 2.5-hour interactive training session on how to use the Serious Illness Conversation Guide; sessions included practice using the guide with an actor and teaching on how to document conversation in the EMR. For deceased patients only, we conducted a chart review to identify the first documented goals-of-care conversation between January 1, 2014 (study start) and date of death. Only conversations with members of their primary care team were analyzed; dates of conversations were recorded.

Of the 101 deceased patients who were selected in the intervention clinics, 63 (62.4%) had documented conversations, compared to 33 (42.9%) of the 77 in the clinics that were not trained. For eligible patients in the intervention population who had a documented conversation, these took place an average of 139.5 days before death (SD: 123.4) as compared to 116.1 days before death (SD: 92.2) in the control population. Analysis is currently in progress to see if conversations in the intervention population were also of higher quality and are more retrievable in the EMR.

This analysis demonstrates that the Serious Illness Care Program may be effectively implemented in a high-risk care management program in the primary care setting to deliver more conversations to patients earlier in the course of their illness. This study was conducted at a single institution; however it is similar in structure to other primary care practices and care management programs. Although further randomized implementation studies are needed to confirm our results, this early data shows the program is feasible in a primary care setting and suggests there may be benefits from a structured intervention to increase conversations around serious illness in clinical settings.
Patient Satisfaction and its Relation to Perceived Visit Duration with a Hand Surgeon

Raymond C. Parrish II
Harvard Medical School, Francis Weld Peabody Society, Class of 2018

David C. Ring, MD, PhD
Hand and Upper Extremity Service, Department of Orthopaedic Surgery, Massachusetts General Hospital

Patient satisfaction is an increasingly emphasized measure of patient-centeredness and an important component of reimbursement programs. Satisfaction has been found to be positively associated with visit duration in the context of primary care but not in ambulatory orthopaedics, though previous studies have focused on actual visit duration rather than perceived visit duration. We herein aimed to determine whether patient perception of time spent with a hand surgeon relates to patient satisfaction after a single new patient office visit.

Prior to each visit, 112 consecutive new patients predicted how much time they expected to spend with the surgeon. Following the visit, patients were asked to estimate the time spent with the surgeon, indicate whether the surgeon appeared rushed, and rate their overall satisfaction with the surgeon. Wait time and actual visit duration were measured. Patients also completed a sociodemographic survey, the Consultation and Relational Empathy (CARE) Measure, the Newest Vital Sign (NVS) health literacy test, and 3 Patient-Reported Outcomes Measurement Information System (PROMIS)-based questionnaires: Upper-Extremity Function, Pain Interference, and Depression. Multivariable logistic and linear regression models were used to determine predictors of patient satisfaction, patient-perceived surgeon rush, and high previsit expectations of visit duration.

Patient satisfaction did not correlate with actual visit duration ($r=-0.010$, $p=0.92$) and did not correlate with perceived visit duration ($r=0.12$, $p=0.21$). Dissatisfaction was independently predicted by both lower patient-rated surgeon empathy (OR 0.82, 95% CI 0.75-0.90; $p<0.001$) and greater symptoms of depression (OR 1.1, 95% CI 1.0-1.2; $p=0.008$). Neither visit duration ($p=0.26$) nor previsit expectations of visit length ($p=0.40$) were determinants of patient-perceived surgeon rush; only surgeon empathy was associated (OR 0.86, 95% CI 0.79-0.94, $p=0.001$). Less educated patients anticipated needing more time with the surgeon (OR 0.82, 95% CI 0.67-0.99, $p=0.044$).

Patient satisfaction with the surgeon and with the time spent during the office visit was primarily linked to surgeon empathy rather than to visit duration or previsit expectation of visit length. Efforts to make hand surgery office visits more patient centered should focus on improving dialogue quality, and not necessarily on making visits longer.
Evaluation Of A Diabetes Performance Improvement Initiative In Primary Care

Achyut Patil
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018
Robert A. Gabbay, MD, PhD
Department of Endocrinology
Joslin Diabetes Center

Diabetes mellitus presents increasingly commonly, placing an important burden on healthcare systems and providers. While endocrinologists are trained in the specifics of diabetes care, the burden of care falls predominantly on primary care physicians, who may lack time, a specialized support staff, and specialized training and knowledge.

The Joslin PRIME program combines elements of multiple types of initiatives to improve patient outcomes and primary care physician performance: iterative quality improvement, audit and feedback, and CME initiatives. Each participating primary care practice undergoes training, and then implements its own 6 month quality improvement initiative.

In this project, we aim to evaluate whether the Joslin PRIME program is effective in improving patient outcomes and altering practice structure for enhanced patient care.

To date, semi-structured interviews have been performed to gain qualitative feedback about the program from participants in Ohio’s Kettering Provider Network. This information, along with early survey data, was used to guide early qualitative changes to the program. In October 2015, this will be combined with quantitative data. Re-assessment of practices’ scores on the JCAT Analytic Tool (a Joslin clinical performance assessment tool that stratifies patients by disease severity) as well as re-assessment of scores on the program’s Office Assessment Test, will further evaluate improvement in patient outcomes and office practices.

Current results are preliminary but indicate that the program has been successful in restructuring practices into team-based practices, distributing the burden of care. Interviews also showed that some aspects of the program required immediate change – participants noted a lack of prior knowledge and training about the quality improvement process, an integral part of the Joslin PRIME intervention. These results led to the addition of more specific quality improvement project guidelines and the addition of new measures for evaluation. Coming results will result in similar re-evaluation and improvement in program structure.

The study is currently limited by a small sample size of 6 participating practices, a current lack of quantitative data to assess practice improvement, and the initially relatively free structure of the PRIME program (the program runs somewhat differently for each practice). However, the program is set to expand to other practices, and quantitative data (JCAT and Office Assessment results) will be available in October to add to the current qualitative results – and the results of this project can be used to provide structure to the program.
Transcriptional Co-activator PGC1alpha Protects Cartilage from Osteoarthritis

Elizabeth Perry
Harvard School of Dental Medicine, Oliver Wendell Holmes Society, Class of 2018

Pere Puigserver, PhD
Department of Cancer Biology
Dana Farber Cancer Institute

Osteoarthritis is the most common joint disorder in the United States, affecting 10% of men and 13% of women aged 60 or older. Osteoarthritis is the degeneration of joint cartilage due to age-related changes as well as injury. The formation of cartilage is driven by transcription factor SOX9. Previous studies have demonstrated that transcriptional co-activator, PGC1a, binds to SOX9 to drive cartilage formation.

The aim of our study is to investigate PGC1a as a target in preventing cartilage degradation. Cells from the MC615 chondrogenic cell line were transfected with a lentiviral doxycycline-inducible vector carrying PGC1a. Cells were seeded in BMP2 to promote chondrocyte differentiation. On days 1-3, cells were treated with doxycycline to allow for PGC1a overexpression. After 3 days, cells were harvested and gene expression measured by qPCR. Doxycycline treated cells were remarkable for a 44-fold increase in PGC1alpha expression and a significant decrease in MMP13 expression, which codes for the protease that degrades collagen-2 protein, the major protein component of cartilage. In addition, cells were stained with Alcian Blue, which stains sulfated proteoglycans. Doxycycline treated chondrocytes were found to have increased matrix staining as a result of increased aggrecan expression. Although much work remains in order to understand the mechanism by which PGC1alpha may protect cartilage form degeneration, the preliminary findings suggest a role for PGC1alpha activation in the treatment of OA.
Effect of Social Media on Dissemination of Preventive Oral Health Measures Through Accessible Online Learning Modules in Rwanda

Yasameen E. Pirooz
Harvard School of Dental Medicine, Francis Weld Peabody Society, Class of 2018

Brittany Seymour, DDS, MPH
Department of Oral Health Policy and Epidemiology
Harvard School of Dental Medicine

Around the world, society is facing revolutionary technological advances and globalization, permitting rapid information transfer. With the evolving technological landscape, media modalities are having a new and emerging impact on health through influencing individual health behaviors, policy decisions, foundation funding, and programs.

These programs can be especially useful in disseminating information in areas where there is a paucity of healthcare providers, such as in Rwanda, where there are no rural dentists and around 35 dentists for the entire country of nearly 12 million, a shockingly low number to adequately provide quality dental care. Further, Rwanda’s president – deemed the “digital president” – has worked with the Rwandan government to advocate the use of social media in the realm of promoting good governance and service delivery.

With that in mind, we worked with students and faculty from the University of Rwanda-School of Dentistry to develop the aims of the project, which were first, to create specific, culturally sensitive objectives for an accessible series of educational oral health modules in Rwanda, and second, to translate the objectives into an online learning module linked to the University’s website, as well as to larger social media outlets such as Facebook and Twitter.

Throughout seven weeks working with a team of four students from the School of Dentistry in Kigali, Rwanda, we created educational modules in both English and Kinyarwanda, which integrated a medley of interactive features including games, videos, and audio clips. Information was gathered through a thorough literature search and empirically supported themes based on the literature search, and was then vetted with our Rwandan partners for cultural appropriateness. The first section of the module connects the relevance of oral health to overall health, emphasizing the importance of good oral health, and shows consequences of oral disease. The second section presents maintenance of good oral health through basic oral hygiene techniques. The third section instruction on the importance of healthy nutrition on oral health. The fourth section discusses the role of dental therapists and surgeons in Rwanda and the module concludes with a summary on the main concepts.

Our module is to be published on the University of Rwanda’s website, as well as broadcasted across the patient waiting rooms at the medical facilities there, with a broader dissemination plan for the future. Limitations encountered included learning the necessary technological skills, understanding terms and practices in oral hygiene in Rwanda, and language barriers within our team.
Maternal Experiences of Racial Discrimination and Offspring Sleep in The First 2 Years of Life

Chloé Powell
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

Matthew W. Gillman, MD, SM
Obesity Prevention Program, Department of Population Medicine
Harvard Medical School and Harvard Pilgrim Health Care Institute

Poor sleep during infancy is associated with adverse childhood health outcomes including increased weight gain in infancy, greater risk for childhood overweight, and behavioral problems. In the United States, black, Hispanic, and Asian infants sleep fewer hours per day than whites. Racial discrimination is linked to shorter sleep duration in adults; however, there are no data examining maternal experiences of racial discrimination and infant sleep duration.

The purpose of the study was to examine the association of maternal lifetime experiences of racial discrimination with offspring sleep duration over the first 2 years of life. We analyzed data from Project Viva, a pre-birth cohort study. We restricted analyses to 552 black, Hispanic, Asian, and “other” non-white mother-infant pairs. During pregnancy, using the Experiences of Discrimination survey, mothers reported lifetime experiences of racial discrimination in each of 8 domains. We categorized responses as 0, 1-2, or ≥3 domains. At children’s ages 6 months, 1 year, and 2 years, mothers reported the number of hours their children slept in a 24-hour period. Our main outcome was weighted average of daily sleep across the first 2 years of life.

Thirty percent of participants reported 0 domains of racial discrimination, 35% reported 1-2 domains, and 34% reported ≥3 domains. Black participants reported more domains of racial discrimination than participants from other racial/ethnic groups and also reported experiencing more racial discrimination for each situational domain. Mothers reporting ≥3 domains of racial discrimination had infants that slept a mean (SD) duration of 11.5 (1.3) h/d from ages 6 months to 2 years, while mothers reporting 0 domains had infants that slept a mean (SD) duration of 11.8 (1.3) h/d. Compared with children whose mothers reported no discrimination, those whose mothers reported ≥3 domains had shorter sleep duration (β -0.31 h/d, 95% CI: -0.62 to 0.00). After adjusting for maternal race/ethnicity, education, income, pre-pregnancy BMI, marital status, smoking history, childcare outside of the home, and urbanicity, the association was attenuated (β -0.19 h/d, 95% CI: -0.52 to 0.14). In post hoc analysis at 6 months, 1 year, and 2 years separately, we found the largest association at 6 months (adjusted β -0.79 h/d, 95% CI: -1.40 to -0.18), and very little by 2 years (adjusted β 0.10 h/d, 95% CI: -0.33 to 0.52).

In conclusion, maternal lifetime experiences of racial discrimination were associated with shorter sleep duration the first 2 years of life; the greatest reduction occurred in the first 6 months. Although further studies are needed to examine the mechanism for such an association, our study suggests racial discrimination might contribute to the racial/ethnic differences in infant sleep duration.
Transcriptome Analysis of Wnt Signaling Pathway in Pediatric Hepatocellular Carcinoma

Naveed Rabbani
Harvard Medical School, William Bosworth Castle Society, Class of 2018
Alexandra J. Miliotis Fellowship in Pediatric Oncology

Khashayar Vakili, MD
Department of Surgery
Boston Children’s Hospital and Harvard Medical School

Pediatric hepatocellular carcinoma (HCC) is associated with high mortality partly due to the lack of effective chemotherapy. Therefore, elucidation of HCC tumor biology and identification of therapeutic targets is critical. The Wnt/β-catenin signaling pathway is essential for proper cellular differentiation and tissue homeostasis. However, its dysregulation has been implicated in adult HCC tumorigenesis, which often arises in the background of cirrhosis. Conversely, comparable biological studies into the pathophysiology of pediatric HCC, which typically occurs without cirrhosis, are lacking. We therefore sought to examine whether the Wnt pathway is also altered in pediatric HCC.

Next-generation sequencing of messenger RNA and exonic DNA from HCC tumor and non-neoplastic liver tissue from 3 pediatric patients was performed. The patients were 1.5, 13, and 13 years old and did not have underlying cirrhosis. Sequenced reads were mapped to the human genome (Genome Reference Consortium Human Genome Build 38). RNA-seq data was used to calculate normalized mRNA transcript expression levels. Differential expression analysis was performed, comparing normal tissue expression levels to tumor. P-values were calculated by fitting the data to a negative binomial distribution and correcting for multiple hypothesis testing. Whole exome sequencing data was used to identify stop-gain and non-synonymous somatic mutations in the protein-coding regions of the genome.

RNA-seq analysis demonstrated a statistically significant increase in the expression of key pro-proliferative proteins of the canonical Wnt pathway, including \textit{WNT1}, \textit{WNT10B}, and Wnt-receptor \textit{FZD10}, in the tumor compared to non-neoplastic tissue. Additionally, there was a significant decrease in several pathway inhibitors including \textit{SFRP5}, \textit{TBL1Y}, and \textit{WNT11} (p-values < 1.0x10^{-4}). Whole exome sequencing of one tumor sample also revealed a previously-reported gain-of-function p.S45F \textit{CTNNB1} mutation.

Our results demonstrate a significant increase in the expression of pro-proliferative genes with a concomitant decrease in the expression of inhibitory genes of the canonical Wnt pathway in pediatric HCC tumors. These findings suggest that the Wnt pathway may provide a potential therapeutic target for the treatment of pediatric HCC. Future studies will focus on increasing the sample size as well as identifying other pathological signaling pathways which may crosstalk with the Wnt pathway.
The Impact of Early Intervention on the Outcomes after Decompressive Craniectomy for Stroke: A Nationwide Analysis

Faith C. Robertson
Harvard Medical School, William Bosworth Castle Society, Class of 2018

William B. Gormley MD, MPH
Director, Neurosurgical Critical Care, Brigham and Women’s Hospital
Director, Performance Improvement, Brigham and Women’s Hospital
Assistant Professor, Harvard Medical School

Decompressive hemicraniectomy (DHC) has been shown to be an effective treatment for space-occupying, malignant cerebral artery infarction, as it decreases intracranial pressure and decreases risk of transtentorial herniation, brainstem compression, and death. However, details surrounding patient selection and appropriate timing of intervention remain controversial. Although evidence supports the performance of cranial decompression for malignant cerebral infarction within 48 hours of presentation, no nationwide analysis has evaluated the predictors of undergoing early intervention in the United States.

Data were extracted from the Nationwide Inpatient Sample (2002-2011). Patients with a primary diagnosis of an anterior circulation acute ischemic stroke who underwent cranial decompression with or without lobectomy were included. Multivariate regression analysis evaluated independent predictors of undergoing early intervention (within 48 hours of admission): potential predictors evaluated included patient sex; admission year; comorbidities; stroke risk factors (atrial fibrillation, cardiac valvular disease, carotid stenosis, carotid dissection, and hypercogulability); longterm antithrombotic medication usage; treatment variables (including the administration of intravenous thrombolytics, interventional stroke therapy, and ventriculostomy placement); cerebral herniation; and hospital characteristics including size, teaching status, and region.

1,432 admissions were included, of whom 53.3% (n=763) underwent surgery within 48 hours. Atrial fibrillation, anticoagulation usage, and teaching hospital admission were associated with an increased odds of undergoing early surgery ($P<0.02$); age greater than 70 years, cardiac valvular disease, diabetes, and carotid stenosis were associated with a lower odds of early intervention ($P<0.03$). No significantly different adjusted odds of in-hospital death were seen based on the timing of intervention (Odds Ratio (OR): 1.12, 95% Confidence Interval (CI): 0.85-1.46, $P=0.43$). However, early intervention was associated with lower adjusted odds of undergoing a tracheostomy or gastrostomy (OR: 0.75, 95% CI: 0.60-0.94, $P=0.001$) and of a hospital stay of at least 24 days (OR: 0.62, 95% CI: 0.47-0.85, $P=0.002$).

In this nationwide analysis, patient age, stroke etiology, and hospital characteristics were associated with differential odds of undergoing early surgery. Although early intervention was not associated with improved mortality, superior outcomes were seen favoring early surgery on some measures including tracheostomy or gastrostomy placement and length of stay.
Copy Number Variation Contributes to the Phenotypic Variability of Syndromic Duane Retraction Syndrome

Victoria K. Robson
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018
Howard Hughes Medical Institute Summer Medical Fellow

Elizabeth C. Engle, MD
Departments of Neurology and Ophthalmology, Boston Children’s Hospital
Investigator of the Howard Hughes Medical Institute

Congenital cranial dysinnervation disorders (CCDDs) comprise a set of diseases caused by aberrant development of the cranial nerves innervating ocular and facial muscles. The most common CCDD is an eye movement disorder called Duane Retraction Syndrome (DRS). In DRS, the sixth cranial nerve fails to reach the lateral rectus muscle, which is instead aberrantly innervated by the third cranial nerve resulting in abduction/adduction deficits and globe retraction on attempted adduction. DRS can be inherited or sporadic and often presents as part of a more complex syndromic phenotype.

The Engle lab previously reported dominant mutations in SALL4 and CHN1 as genetic causes of DRS that perturb sixth nerve development, providing insights into molecular mechanisms of motor neuron development and cranial axon guidance. While the etiology of most DRS cases remains unknown, rare reports of simplex syndromic DRS implicate de novo copy number variants (CNVs). Thus, we conducted CNV analysis of a cohort of patients with syndromic DRS to identify new causal genes and more precisely define phenotype-genotype correlations.

From a cohort of 500 genetically undefined DRS probands, we selected 84 simplex probands with syndromic DRS to phenotype and group into overlapping clinical categories, including abnormalities of additional cranial nerves, CNS, PNS/muscle, skeleton, face/limb morphology, craniofacial development, and other organs. From among these, 31 trios were selected for initial CNV analysis. Whole genome single nucleotide polymorphism (SNP) data were generated with the Illumina Human Omni2.5 + Exomes BeadChip array. Using the PennCNV algorithm, a total of 363 de novo CNVs (257 deletions, 106 duplications) were detected in the probands. CNVs were subsequently validated using PennCNV quality control metrics, a visual scoring protocol, and the cnvPartition algorithm. Notably, two probands with similar complex phenotypes have overlapping 7 Mb terminal 10q26 deletions while a third with a milder phenotype has a smaller 11 Kb deletion in this region.

Overall, we have developed a novel pipeline for systematic phenotyping and CNV analysis of DRS. Our data suggest an enrichment of de novo deletions without specificity for genomic location in a population of syndromic DRS probands with highly complex and overlapping phenotypes. The diversity of associated de novo CNVs therefore may contribute to the phenotypic heterogeneity of these patients. Moreover, 10q26 is a promising region for future investigation. This study is limited in terms of procurement of sufficient clinical data and samples. Further work will attempt to confirm candidate CNVs through screening the larger DRS cohort.
Neutrophil-mediated Dermatoses in Neutropenic Patients

George A. Romar
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Sherrie J. Divito, MD, PhD
Department of Dermatology, Brigham and Women’s Hospital
Harvard Medical School

Patients with hematologic malignancies are often treated with chemotherapeutic agents designed to eliminate malignant white blood cells (WBCs) but, in so doing, destroy benign WBCs as well. It is assumed that these chemotherapeutic agents destroy WBCs in peripheral tissues, such as skin, in parallel to WBCs in blood and bone marrow. Anecdotally, however, profoundly leukopenic patients sometimes develop WBC-mediated skin disease, suggesting that skin WBCs may survive chemotherapy. Importantly, if chemotherapeutics fail to eliminate skin WBCs, malignant WBCs in skin could serve as reservoirs of disease. To begin to address this, we sought to investigate the development of neutrophil-mediated dermatoses in neutropenic patients.

We designed a retrospective cohort study to compare development of neutrophil-mediated dermatosis in patients who are moderately/severely neutropenic – defined as an absolute neutrophil count < 1x10^3/μL – with those who are not. The study population included adult inpatients at Brigham and Women’s Hospital for whom the dermatology service was consulted for rash between June 2009 and December 2011. Only patients for whom a skin biopsy was obtained and read by a board-certified dermatopathologist and for whom a peripheral WBC count with differential was taken on the same day as the biopsy were included. Patients for whom a single lesion was biopsied on suspicion of cutaneous malignancy were excluded.

Two hundred thirty patients met these inclusion/exclusion criteria. Forty-nine patients were moderately/severely neutropenic on the day of skin biopsy; 28 females and 21 males. Median age was 57 (range 22-74). Seven patients had pathology-confirmed neutrophil-mediated dermatosis (incidence=14.3%). Comparatively, there were 181 patients in the control group: 98 females and 83 males, with median age 57 (range 19-94). Of these, 34 had pathology-confirmed neutrophil-mediated dermatosis (incidence=18.8%). The relative risk of developing a neutrophil-mediated dermatosis with moderate/severe neutropenia compared to controls was 0.7605 (95% CI 0.359, 1.609).

Our preliminary results suggest that moderate/severe neutropenia does not preclude development of neutrophil-mediated dermatoses. The moderate/severe neutropenia group showed slightly reduced likelihood of developing a neutrophil-mediated dermatosis compared to controls, though the results were not statistically significant. This may be due to small sample size, limiting the study’s power. We are currently expanding our study sample to overcome this limitation. Further, we are analyzing whether treatment with granulocyte-colony stimulating factor increases the risk of developing a neutrophil-mediated dermatosis and whether development of such rashes correlates with or predicts recovering neutrophil counts post-chemotherapy. Finally, we are performing a parallel investigation of lymphocyte-mediated dermatoses in lymphopenic patients.
An Exploration of the Oral Health Knowledge, Attitudes and Behaviours about School-based Oral Health Education of 11-14 Year Old School Children

Sara Rosenberg
Harvard School of Dental Medicine, Oliver Wendell Holmes Society, Class of 2018

Sally Weston-Price, BDS, MSc, DDPH, RCS
Dental Public Health Department, Institute of Dentistry, Barts and the London School of Medicine & Dentistry, Queen Mary University of London

Inequalities in dental caries remain globally, despite prevention efforts and advancements in dentistry. New techniques for preventing dental caries at the public health level need to be evidence-based and address inequalities. One emerging method of dental caries prevention in children is web-based health educational tools aiming to reach ethnically diverse student populations. e-Bug (www.e-bug.eu) operated by Public Health England provides such a website offering health-related education to school children across Europe.

Like many resources the current e-Bug Oral health module focuses on younger children but is not designed for interactions with adolescents, and specifically those aged 11-14. Adolescent behaviours vary dramatically from those in early childhood. Therefore, research focused on age specific dietary habits, oral hygiene practices, and oral disease risk factors along with the baseline oral health knowledge is required, so that age appropriate oral health educational materials can be developed and implemented.

This qualitative study aims to address the gaps in our understanding about the oral health knowledge, behaviours, and attitudes of 11-14 year old school children. Gaining a better understanding about this group will help inform the development of an e-Bug oral health education module designed for them.

Six focus groups, consisting of students aged 11-14, taught at Key Stage 3 level in the Greater London area were conducted during July 2015. Three focus groups per school organised by age and containing 4-5 students (aged 11-12, 12-13, or 13-14 years) were directed. Issues surrounding oral health related behaviours, attitudes, and education were discussed, audio recorded and transcribed. Thematic analysis was performed involving transcript coding, theme identification, and data interpretation.

Our results showed that whether students performed healthy or unhealthy oral hygiene behaviours was influenced by their current oral health knowledge and attitudes, which were ultimately informed by their sources of oral health information. Our focus groups identified two emerging sets of student perceived behaviour drivers behind healthy and unhealthy oral hygiene habits. The recurrent themes that drove students to practice healthy oral hygiene behaviours were parental pressures, cleanliness, fear, the media, appearances, orthodontic treatment, and pain. Whereas those factors perceived to drive unhealthy oral hygiene behaviours were time pressures, apathy, or “unknown.” This approach revealed insights that help understand what 11-14 year olds think is driving their oral health behaviours and practices. Further research should consider how an e-Bug module can be developed to utilise these self-perceived drivers to motivate this specific age group to change their oral hygiene behaviours.
Risk of Rupture of Intracranial Aneurysms: A Systematic Review and Meta-analysis by Aneurysm Location

Robert F. Rudy
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018
Neurosurgical Research and Education Foundation Medical Student Summer Research Fellowship

Rose Du MD PhD
Department of Neurosurgery
Brigham and Women’s Hospital

The optimal management of unruptured intracranial cerebral aneurysms requires risk-stratification based on the probability of developing aneurysmal subarachnoid hemorrhage. The risk of morbidity and mortality from aneurysm rupture must be weighed against the potential for periprocedural complications associated with endovascular or microsurgical aneurysm obliteration. Accurate, robust prediction of the risk of aneurysm rupture is paramount for cerebrovascular surgeons when considering the best management strategy for each individual patient.

Although prior meta-analyses have identified patient and aneurysm characteristics as predictors for aneurysm rupture and have informed the guidelines for management of unruptured aneurysms, these studies have not stratified risk of rupture by arterial location. However, the relative impact of different risk factors may vary with aneurysm location. In this study, we sought to assess predictors of aneurysm rupture in specific arteries by conducting a systematic review and meta-analysis and evaluating known predictors of rupture when stratified by individual cerebral arteries. Specifically, we are interested in determining the ability of aneurysm size and morphology to predict rupture risk for aneurysms located in the anterior communicating artery, internal carotid artery bifurcation, middle cerebral artery, posterior communicating artery, and basilar artery. We hypothesized that differences in size and morphology of aneurysms when predicting risk of aneurysm rupture in different intracranial locations will differ substantially and be uniquely defined.

The Medline, EMBASE, and Cochran databases were queried through May 5th, 2015. Search results were extracted into Endnote X7 (Thompson Reuters, New York, New York) and combined. Duplicates were deleted using the EndNote duplicate tool and by manually checking. 7,162 studies after duplicate deletion were included. Screening was performed using the study abstract, when available; in the absence of an abstract, study relevance was determined by title. Any study deemed potentially relevant was included at this stage for further review. 800 studies were determined relevant and advanced to the next stage of review.

Following abstract screening, each individual study will be obtained in full. Thereafter, meta-analysis inclusion will be determined based on predetermined criteria, pertinent data will be extracted, and statistical analysis will be conducted in STATA 13 (StataCorp LP, College Station, Texas). While still underway, this project aims to provide superior understanding of the risk of rupture of intracranial aneurysms in specific arterial locations.
Development of a Web-Based Resource Directory for Improving Pediatric to Adult Healthcare Transitions in the Medical Home

Priyanka Saha
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Kitty O’Harc, MD
Internal Medicine and Pediatrics, Boston Children's Hospital

While over 90% of youth with special health care needs (YSHCN) now survive into adulthood, only 40% of these youth receive all of the services they need to complete a successful transition to adulthood (1). Providers cite major barriers including lack of time to adequately address transition needs, inadequate knowledge of services needed for successful transitions, and insufficient coordination between care providers (2).

In order to eliminate the knowledge gap faced by families and providers about transition resources, we are developing an online transition resource directory. HelpSteps (www.helpsteps.com) is an existing web-based tool developed at Boston Children’s Hospital to connect families with local social service agencies (3). We are developing a transition component of HelpSteps, which will serve as a centralized resource for patients, families, and providers during transition planning.

A convenience sample of Boston Children’s Hospital staff was surveyed as to the agencies they utilize most frequently as part of transition planning. Additional resources were identified at a community resource fair targeting YSHCN and their families. These agencies were then contacted by phone for further details about the services provided. Agency listings were grouped in a structured manner into the existing HelpSteps online platform, using fixed subcategories. Through either the guided search or direct search features on the website, patients and providers can indicate their preferences for resources pertaining to such categories as living assistance, job support, insurance and financial support, and more. Users are then led to a list of local agencies that provide the services relevant to their preferences.

We have begun to collect qualitative feedback from potential users including YSHCN, families and providers to assess ease of use of the directory and applicability to needs. We will pilot the HelpSteps transition directory in a primary care medical home, as part of a team-based approach to transition care. The ultimate goal is to integrate the use of HelpSteps into clinical programs to improve the identification of transition resources for YSHCN.
A Retrospective Single-Center Study on Patient Outcomes Following Total Temporomandibular Joint Replacement Surgery

Rohit Sahdev
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

David A. Keith, DMD
Department of Oral and Maxillofacial Surgery
Massachusetts General Hospital

Total joint replacement (TJR) surgery is normally reserved for patients with end-stage TMJ disease including, but not limited to, an original diagnosis of the following: congenital abnormalities, growth disorders, infections, fractures, tumors, arthritis, ankylosis, dislocations, internal derangement, etc. Patients requiring TJR surgery have often undergone several previous non-invasive and surgical treatments, all of which have been unsuccessful. These patients remain functionally affected and typically present with chronic TMJ pain, limited range of motion and facial deformities. The goal of TJR surgery is to reduce pain, reestablish a functional TMJ with improved range of motion and correct any facial deformities. Historically, prosthetic reconstruction of the TMJ has been plagued with device failures and complications, including heterotopic bone formation, pain and foreign body formations.

In this retrospective cohort study we conducted a chart review of 95 patients to assess treatment outcomes and the potential risks and benefits involved. The objective of this study was to evaluate the outcomes of patients who underwent TJR surgery at Massachusetts General Hospital over the last 15+ years with the overall goal of identifying predictor variables associated with successful outcomes and those associated with treatment failure by using univariate and multivariate analysis. Predictor variables included total TMJ replacement, patient related variables such as age, duration of disease, original diagnosis, prior treatments, previous operations (number and type), preoperative pain levels, preoperative range of motion, preoperative occlusion. Outcome variables included postoperative pain levels assessed by VAS/questionnaire, postoperative range of motion, postoperative occlusion, and postoperative complications.

The study sample was composed of 95 patients (85 female and 10 male) with a mean age of 44 years who had a total of 177 total joint replacement prostheses placed between 2000-2015 and who had at least 6 months of follow-up post surgery. The main diagnoses that resulted in total joint replacement were inflammatory disease and ankylosis. Preoperatively, the mean maximal incisal opening was 25mm and the mean pain score on the visual analog scale was 6. Postoperatively, patients had a mean increase in range of motion by 7mm and a decrease in pain by 2. Of note, 55% percent of patients reported a decrease in pain and 71% of patients reported an increase in range of motion.

This was one of the largest studies (n=95) evaluating the outcome of TJR surgery. The results demonstrate the effectiveness of total joint replacement surgery and describe the MGH experience over the past 15 years. We are currently in the process of evaluating the predictor factors using univariate and multivariate analysis.
Post-Operative Stability of Distraction Osteogenesis of the Mandible

Alfonso Salcines
Harvard School of Dental Medicine, Oliver W. Holmes Society, Class of 2018

Zachary S. Peacock, DMD, MD, FACS
Department of Oral and Maxillofacial Surgery
Massachusetts General Hospital

Distraction osteogenesis (DO) has become a reliable technique for correcting craniofacial deformities through skeletal expansion. As DO requires a mandibular osteotomy followed by gradual lengthening, the existing or developing dentition can be affected. Controversy exists as to whether the distracted mandible continues to grow. The purpose of this study is to determine the affect of DO on the dentition and residual mandibular growth.

This is a retrospective study assessing all pediatric patients undergoing mandibular DO between 1998-2014 at Massachusetts General Hospital. Those with adequate follow-up and complete clinical and radiographic records were included. Adverse affects on the development, eruption, and morphology of the dentition were quantified by comparing panoramic radiographs at each time point. Post-treatment mandibular growth was quantified by comparing lateral cephalograms at device removal or the end of the distraction period with 1 year and longest follow-up.

When assessing the dentition, 19/22 (86%) subjects had unresolved complications involving the dentition at the time of the last follow-up. 37/85 (43%) mandibular molars had been affected by DO. Of these, 14 had damage to the crown or root by the osteotomy, 9 failed to erupt when expected, 16 had abnormal spacing.

Twenty-nine subjects were included in the mandibular growth assessment. Of these, 12 and 17 subjects underwent mandibular body and ramus DO, respectively. After mandibular body DO, there was a decrease of 2.36 (±7.61) mm in length (Gonion to Gnathion) at 1 year and an increase of 2.76 (±5.52) mm at longest follow-up (5.75 ± 3.17 years). After mandibular ramus DO, there was a decrease of 4.37 (±6.91) mm in length (Articulare to Gonion) at 1 year and an increase of 0.99 (±7.51) mm at longest follow-up (6.33 ± 1.92 years).

The results of this study suggest mandibular DO has a significant adverse affect on the dentition. After a period of relapse, there is continued growth of the both the mandibular body and ramus after DO.
A Volumetric MRI Study of the Basal Ganglia in Geriatric Patients with Bipolar Disorder

Christine K. Santiago
Harvard Medical School, William Bosworth Castle Society, Class of 2018
Neil Samuel Ghiso Fellowship

Brent P. Forester, MD, MS
Department of Geriatric Psychiatry
McLean Hospital

David G. Harper, PhD
Department of Geriatric Psychiatry
McLean Hospital

Bipolar Disorder is a severely debilitating psychiatric disorder that affects 5.7 million American adults. In geriatric populations, bipolar disorder affects approximately 1.4 million elderly. Bipolar disorder causes unusually large fluctuations between manic and depressed mood states resulting in functional and cognitive impairment. Because of suicide and comorbid medical ailments such as obesity, type-2 diabetes and cardiovascular disease, life expectancy in bipolar disorder patients is 30% shorter than the general population. Despite excess mortality, recurrent episodes of mania and depression persist into later life with adverse affects on cognition, daily functioning and quality of life.

Currently bipolar disorder is diagnosed using clinical criteria defined in the DSM 5. However, neuroimaging could be a tool for more accurate and earlier diagnosis. Discovering brain regions involved in bipolar disorder may also direct novel therapeutic interventions. Previous cross-sectional neuroimaging studies have found structural changes in the cortical, subcortical and limbic brain regions of bipolar patients. Studies regarding the globus pallidus are limited and findings inconsistent.

The aim of this study was to use enhanced MRI imaging methods to determine volumetric group differences in the basal ganglia, globus pallidus and caudate nucleus between geriatric bipolar subjects and controls. We hypothesized a 337 mm³ volumetric decrease in these brain regions for bipolar subjects with 80% power, p < 0.05 and 15 subjects per arm. To test this hypothesis we did a retrospective study using MRI imaging collected with a Siemens 3T Trio scanner equipped with a 32-channel, phased array coil. We used FSL software for volumetric analysis of T1 weighted images and JMP Pro 10 for multiple regression analysis with diagnosis and total brain volume set as predictors. p< 0.05 was considered statistically significant. Interim analysis did not show a statistically significant volumetric difference between bipolar (n=10) and controls (n=11) in the globus pallidum, caudate or basal ganglia regions ((t(18)=0.62; p=0.5413); (t(18)=1.13; p=0.2731) and (t(18)=1.37; p= 0.1877), respectively). However, all three regions demonstrate a trend toward lower volumetric sizes in bipolar patients (globus pallidum: controls= 3710.10 mm³, bipolar= 3548.17 mm³; caudate: controls= 6732.34 mm³ bipolar= 6343.04 mm³; basal ganglia: controls= 70539.70 mm³ bipolar= 6684.10 mm³).

In conclusion, volumetric differences in the globus pallidus, caudate and basal ganglia regions were not statistically significant between bipolar patients and normal controls. A small sample size may have limited our power to detect group differences in basal ganglia volume. Next steps planned are to increase the sample size for follow-up volumetric analyses and then initiate a functional connectivity analysis of motor networks in the basal ganglia region of bipolar patients.
“Ou Menm Ak Kansé”: Developing an Educational Booklet for Patients with Cancer in Haiti

Lauren E. Schleimer
Harvard Medical School, Francis W. Peabody Society, Class of 2018

Lawrence N. Shulman, MD
Deputy Director for Clinical Services and Director of the Center for Global Cancer Medicine
Abramson Cancer Center, University of Pennsylvania

A 2014 review in the Annals of Global Health listed Haiti as the country with the worst cancer survival rates in all of Latin America and the Caribbean. There are just a handful of oncologists serving a country of over 10.2 million, most of whom charge prices most patients cannot afford. In 2011, the Dana-Farber Cancer Institute and Partners in Health established the first cancer program in Haiti’s central plateau, seeking to bring the benefits of modern cancer medicine to those who need it most. There are currently no available materials to educate patients about cancer that are culturally and literacy appropriate for Haiti. We collaborated with the non-profit organization Global Oncology and design firm The Meme to develop, adapt and evaluate a low-literacy educational booklet about cancer for patients in Haiti.

We recruited a representative sample of patients presenting for chemotherapy at the University Hospital in Mirebalais for individual interviews (n=20) and two focus groups (n=16). Interviews contained a pre- and post-intervention knowledge test and qualitative components. Surveys were distributed to providers to assess their priorities for patient education and to specifically evaluate booklet content.

Patients across all levels of education increased their performance on the knowledge test after counseling with the educational materials. The average test score increased from 2.94 to 5.35 out of 8 points total, with larger increases for patients who had not yet received their first cycle of chemotherapy. Two line drawings—Fatigue and Hair Loss—were identified as ineffective since a majority of illiterate or low-literacy patients incorrectly identified the symptom being depicted. Of those patients initially unable to describe the difference between curative and palliative treatment, half were able to correctly describe the difference in post-intervention testing. Patients’ opinion of the booklet was unanimously positive; all participants requested a copy to take home and recommended that we distribute the booklet to all newly diagnosed patients.

Patients’ knowledge and beliefs about cancer vary widely across cultural contexts. It’s essential to develop culturally and literacy appropriate educational materials for patients in resource-poor settings. This pilot study in Haiti can serve as a model for future efforts to develop and adapt patient educational materials for low-resource settings.
In vitro validation of immune resistant genetic changes in cancer

Joseph C. Sedlak
Harvard Medical School, Francis Weld Peabody Society, Class of 2021

Nir Hacohen, PhD
Massachusetts General Hospital
Director, MGH Center for Cancer Immunotherapy

Cancer immunotherapies have greatly improved long-term survival in patients with advanced melanoma. However, response rates remain low (30% to 38%) and those who experience a response are likely to relapse. To improve response rates and reduce relapses, a deeper understanding of the pathways leading to immunotherapy resistance is needed. Our lab aims to better understand immunotherapy resistance by studying the anti-tumor immunity effects of two genes: ALOX15B and CASP8.

Amplifications of ALOX15B and inactivating CASP8 mutations were identified in patient tumors from the Cancer Genome Atlas (TCGA) and correlated with decreased anti-tumor immunity. ALOX15B acts as a tumor suppressor in a number of cancers, but may also have a cancer promoting immunological role. CASP8 is part of the extrinsic apoptosis pathway, one of two major pathways by which cytotoxic T lymphocytes (CTLs) directly kill cancer cells.

To determine the role of ALOX15B and CASP8 in anti-tumor immunity, we are genetically engineering murine B16 melanoma cells, isolating CTLs from OT-I mice, and performing three functional assays. Cell lines are being created using lentiviral transduction of plasmids containing the CRISPR (clustered regulatory interspersed short palindromic repeats) system to express endogenous Alox8 (murine ortholog of ALOX15B) or knockout Casp8 (murine ortholog of CASP8). All cell lines will be transduced with ovalbumin, such that CTLs from OT-I mice will kill cells expressing ovalbumin peptide SIINFEKL bound to the MHC class I allele. We will functionally assay the effects of these perturbations on the cells' doubling time, migration through a basement membrane extract, and change in percentage of live cells after incubation with activated OT-I mouse CTLs. Completion of experiments and results are pending.

Given the roles of ALOX15B and CASP8, we hypothesize that increasing the expression of Alox8 will decrease in vitro proliferation, decrease invasion through a basement membrane, and not affect the ability of CTLs to kill. Conversely, we hypothesize knocking out Casp8 will increase proliferation rate, not affect invasion through a basement membrane, and decrease killing by activated CTLs. These in vitro studies will shed light on how the ALOX15B and CASP8 pathways may be targeted to reduce immunotherapy resistance.

Our study has several limitations, with the main one being an in vitro study design. An in vitro study design cannot fully capture the complex interactions of different cell types found in the immune system. To further validate the roles of ALOX15B and CASP8, future studies should be done in vivo.
Developing preoperative assessments of brain function to improve anesthetic care in elderly patients

Y. Raymond Shao, PhD
Harvard Medical School-Massachusetts Institute of Technology
Irving M. London Society, Class of 2018

Emery N. Brown, MD, PhD
Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology
Department of Anesthesia, Critical Care and Pain Medicine
Massachusetts General Hospital

Everyday in the United States, nearly 100,000 patients undergo general anesthesia and sedation, with a high proportion being the elderly. An important complication for general anesthesia in elderly patients is the risk of developing post-operative delirium (POD) and post-operative cognitive dysfunction (POCD). Given the variability in anesthetic response in elderly patients, it is important to identify people who are at high risk of developing anesthetic-induced delirium and post-operative cognitive dysfunction and who therefore require special anesthetic handling.

A critical gap in the delivery of anesthetic care is the lack of pre-operative or intra-operative biomarkers that can help predict post-operative cognitive changes. General anesthesia represents a major disturbance to brain networks, and the brain’s ability to return to normal cognitive function will likely rely on two factors: the robustness of the brain networks and the level of cognitive reserve. Therefore, pre-operative measurements of brain network robustness and level of cognitive function are good candidates for predicting the outcomes of post-anesthesia cognitive recovery.

Recent studies from our laboratory show that elderly subjects have reduced anesthetic-induced frontal alpha oscillations and an increased probability of experiencing burst suppression during anesthesia. These results suggest that as brain networks deteriorates with aging, the brain is less capable of generating robust oscillations and more likely to enter burst suppression when general anesthetic drugs are administered.

Our working hypothesis is that pre-operative resting-state brain oscillations and cognitive scores are correlated with intra-operative anesthesia-induced brain oscillations and post-operative recovery in elderly patients. The proposed study has three aims. First, we will characterize the relationship between pre-operative resting-state occipital alpha electroencephalogram (EEG) oscillations and pre-operative measurements of cognitive function in elderly patients. Second, we will characterize the relationship between pre-operative occipital alpha EEG oscillations and anesthesia-induced frontal alpha and burst suppression EEG patterns in elderly patients. Third, we will characterize the relationship between pre-operative occipital alpha EEG oscillations and post-operative emergence time and acute cognitive recovery in elderly patients. A major challenge of the study has been to design study procedures in a way that we are not interfering with patient care or clinical flow in the operating rooms and the perioperative spaces. We have received preliminary approval of our Institutional Review Board (IRB) protocol, and we hope to complete a significant portion of patient data collection and analyses over the next six months.
Regional Differences in Caries Prevalence in Icelandic Six Year Olds

Jonathan Shapiro
Harvard School of Dental Medicine, Oliver Wendell Holmes Society, Class of 2018

W. Peter Holbrook, BDS, PhD
Faculty of Odontology
University of Iceland

Previous analyses studying Icelandic oral health showed that caries rates in the mid-1980’s and mid-1990’s differed by child’s place of residence. However, a 2009 study that analyzed data from a national Oral Health Survey (OHS) of 6-, 12-, and 15-year-olds showed that these regional differences disappeared for 12- and 15-year-olds. However, the 6-year olds’ data were not analyzed. The present study examined whether regional differences in caries prevalence in 6-year olds had also disappeared and attempted to identify potential contributing factors to any observed differences.

The 2005 survey dataset included 744 6-year-olds. Subjects’ data were coded for region of dwelling (capital city, fishing villages, farming communities). Information on the dental examination method has been published. Using data from the OHS, the current study assesses caries severity using mean D1-6MFT and D3-6MFT scores. A one-way ANOVA with post hoc testing was conducted to identify any statistically significant differences between regions. Data were analyzed using SPSS (v.23).

Mean D1-6MFT scores (± SD) in Reykjavik, fishing villages, and farming communities were 2.84±3.65, 4.29±4.01, and 2.68±3.94, respectively. Fishing villages had significantly higher caries than Reykjavik (p<0.0001), and the farming communities (p=0.032). However, the higher caries in the capital vs. farming communities was not significant. The same ordinal relationships were observed and followed the same patterns of significance when assessing mean D3-6MFT scores (± SD). Additionally, this study examined whether these regional differences extended to potential contributing factors to caries, such as dietary components (consumption of candy, sugar-containing soda, juices) and oral hygiene habits (brushing, flossing, dentist visits). In general, there were few contributing factors that mirrored regional differences, and several findings suggested that fishing communities had the best oral hygiene and dietary habits.

Although self-reporting bias may have influenced the dietary/hygiene survey results, the regional differences in caries prevalence in 6-year-olds appears to exist. A nationwide reassessment of healthcare policies, public-health education, and access to care may be beneficial. Furthermore, the findings are comparable to other Scandinavian countries where regions of dwelling are analogous to Iceland.
Evaluation of Acute Respiratory Distress Syndrome (ARDS) in Patients Enrolled in the Protocolized Care for Early Septic Shock (ProCESS) Trial

Krishan Sharma
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

Peter Hou, MD
Department of Emergency Medicine
Brigham and Women’s Hospital

Background: Severe sepsis is a systemic disease that develops in as many as 3 million adults in the U.S. each year, resulting in significant morbidity and mortality. Sepsis is the most common etiology of acute respiratory distress syndrome (ARDS), which is associated with a high case-fatality rate. Over the past two decades, however, recent sepsis trials that enroll patients from ED and ICU settings do not explicitly report ARDS incidence.

Aims: The Protocolized Care for Early Septic Shock (ProCESS) trial was a recent multicenter, randomized controlled trial that evaluated the efficacy of protocolized quantitative resuscitation in the treatment of severe sepsis for patients presenting in the ED. Using this data, we aim to conduct a sub-analysis of the ProCESS trial to determine the incidence of sepsis-related ARDS in patients presenting to the ED with severe sepsis. In addition, we will determine if a particular sepsis treatment strategy is associated with the incidence of ARDS. We hypothesize that early aggressive fluid resuscitation with positive fluid balance may be associated with increased mortality in patients with ARDS.

Methods: Relevant physiological variables for ARDS determination have been collected and will be used to screen for subjects who may have developed sepsis-induced ARDS, as defined by the Berlin Criteria. The analysis of this study’s hypothesis will consist of a thorough set of descriptive analyses and the primary test of the hypothesis on the different frequency for ARDS development by treatment strategy.

Results: 47 patients have initially been identified as meeting the oxygenation requirement for ARDS under the Berlin criteria, with a PaO2/FiO2 < 300mm Hg with PEEP > 5cm H2O. Two radiologists will now independently assess the ARDS determination of these subjects by examining their chest X-rays on a secure platform that has already been established. The images have recently been uploaded onto the platform and anonymized. We are now in the process of waiting for the radiologists’ assessment before determining the incidence of ARDS and conducting our descriptive analyses.

Significance: By determining the incidence of ARDS in these patients, we will be able to identify factors that can be used to risk-stratify severe sepsis patients who are at high risk of developing ARDS, including factors at hospital presentation. In addition, our analysis on sepsis treatment strategy affecting ARDS development may guide future treatment strategies for sepsis patients.
A Qualitative Evaluation of Student and Patient Perceptions of a Palliative and End-of-Life Care Curriculum taught in the Nursing Home

Ashley Y. Shaw
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

Kristen G. Schaefer, MD
Department of Adult Palliative Care, Dana-Farber Cancer Institute

Medical trainees continue to receive inconsistent formal training in palliative care and end of life issues, particularly in the outpatient, hospice, and nursing home settings that many patients utilize at the end of life. As U.S. medical students continue to matriculate with increasing amounts of clinical exposure prior to medical school and preclinical curricula are shortened, earlier exposure to end-of-life issues may better prepare students to assist with the challenges faced by seriously ill or dying patients during their clinical rotations and beyond.

Through its ten-week, full-time curriculum, the Columbia University Research Cluster on Science and Subjectivity-ArchCare at Terence Cardinal Cooke (RCSS-TCC) internship provides pre-medical college interns with a patient care and accompaniment experience in nursing home palliative care. This experience is designed to provide exposure to these populations and convey foundational pre-clinical skills essential to medical students preparing for the wards. Although research has been performed to identify palliative care competencies around palliative care for medical students, residents, and fellows, no studies have been performed to evaluate undergraduate college internships with clinical exposure to these populations to identify appropriate competencies.

Our aims were to evaluate the RCSS-TCC internship curriculum in conveying foundational pre-clinical knowledge and skills necessary to achieve medical student-level competencies in palliative care and to assess nursing home residents’ perceptions about students’ impact on quality of life in the nursing home. All four 2015 RCSS-TCC Columbia University interns completed written surveys about their familiarity with palliative care knowledge, skills, and attitudes before and after the internship. We conducted serial semi-structured interviews with each intern asking them to reflect on changes in their knowledge, skills, and attitudes surrounding palliative care since the previous interview. In addition, we asked the students to reflect on the impact of internship on quality of life for nursing home resident. We also conducted one-time written surveys and interviews with nine TCC nursing home residents asking about their perceptions of the internship’s impact on their quality of life.

Written surveys completed by students and nursing home residents and their loved ones will be quantitatively analyzed for Likert score results. Qualitative analysis of semi-structured interviews of student interns and nursing home residents will be performed. Interviews will be analyzed for prevalence and related context of selected words and expressions. Themes surrounding the efficacy of certain curricular components in preparing and motivating pre-clinical students to deliver high-quality palliative care will be identified.
Extracorporeal Immune Modulating Therapy for Sepsis

Andre Shomorony
Harvard Medical School, Irving M. London Society, Class of 2018

Daniel Kohane, MD, PhD
Department of Anesthesiology, Division of Critical Care,
Boston Children’s Hospital

Sepsis affects millions of people, with a worldwide incidence of 18 million cases per year. Sepsis results from an infection that causes an unregulated, systemic inflammatory response, leading to septic shock, multiple organ failure and death. Effective treatment options are limited, and sepsis remains the leading cause of death in critically ill patients in the United States. Attempts to modulate the inflammatory response seen in sepsis have been unsuccessful, perhaps due to the temporally dynamic pathophysiology of the sepsis syndrome. We hypothesized that a successful immune modulating therapy for sepsis must selectively remove deleterious cytokines during the initial inflammatory burst in a time-limited fashion, to avoid long-lasting immune suppression that further exacerbates the immunosuppressed state seen in the later stages of sepsis.

We have developed extracorporeal blood-filtering devices that are surface-modified with antibodies to selectively remove inflammatory cytokines from the blood of septic patients. These devices may be incorporated within existing extracorporeal circuit platforms for convenient and effective filtering. Our first aim was to design, develop and characterize such antibody-modified conduits (AMCs). Each AMC was endowed with a different surface antibody to target a single cytokine, such that multiple AMCs could be incorporated into circuits in modular fashion to remove multiple cytokines. Secondly, we attempted to modulate cytokine concentrations in vivo. We administered TNF-α into rats to elevate their cytokine concentrations and used AMCs to reduce those concentrations to minimal levels.

We have obtained promising preliminary data. We have built AMCs endowed with infliximab (anti-TNF-α antibody) and bevacizumab (anti-VEGF antibody) and tested them for selectivity in different media in vitro. Both in blood and in BSA, the two different AMCs have proven effective in selective cytokine filtration. We have also obtained promising in vivo results. Rats infused with TNF-α for 8 hours have had differential survival depending on whether they were equipped with AMCs; those whose circulation was cleared of TNF-α by infliximab-endowed AMCs survived significantly more than those with control circuits.

Our next step will be to fully develop an animal model of sepsis – with endogenous cytokine release – in which to test our technology. We will use AMCs to modulate in vivo cytokine concentrations and to mitigate the systemic inflammatory response by specific cytokine elimination. If successful, our proposed strategy will not only result in the regulation of the cytokine cascade seen in septic patients, but will allow for a much better understanding of sepsis and of SIRS pathogenesis.
Quality of life assessment following cardiac surgery in a resource-limited setting: Rwanda

Colleen Sinnott
Harvard Medical School, William Bosworth Castle Society, Class of 2018

JaBaris D. Swain, MD MPH
Department of Surgery
Brigham and Women’s Hospital, Harvard Medical School

Despite its near eradication in high-income countries, rheumatic heart disease (RHD) remains the most common acquired cardiovascular disease among children in sub-Saharan Africa, with a prevalence of 6.7 per 1000 in children aged 5-14 years in Rwanda. Many of these children require open-heart surgery to treat critical mitral and aortic valve lesions if left undiagnosed and without prophylactic treatment. In Rwanda there are only 9 anesthetists, 17 general surgeons and four cardiologists to serve a population of more than 12 million; however, unique partnerships with international humanitarian surgical teams provide opportunities for life-saving cardiac surgeries for RHD patients. Little is known about the cost-effectiveness and quality improvement gained from these mission-style surgical interventions.

Assessment of the quality of life following cardiac surgery in Rwanda would help to inform policy regarding the investment of scarce health-care resources in developing long-term domestic provisions for comprehensive cardiovascular care. We sought to quantify the value obtained from cardiac surgical intervention by measuring quality of life among post-cardiac surgery patients in Rwanda.

We administered the Ferrans and Power Quality of Life Index (QLI) tool—Cardiac Version (http://www.uic.edu/orgs/qli/) to 114 patients who had undergone open cardiac surgery for treatment of RHD. Four major domains were considered: Health and Functioning, Social and Economic, Psychological/Spiritual, and Family.

For the entire patient population, the mean total Quality of Life Index score (QLI) was 20.79 ± 4.07 on a scale from 0-30, where higher scores indicated higher quality of life. Women had significantly lower “Social and Economic” subscores (16.81 ± 4.17) than men (18.64 ± 4.10), (p < 0.05). Patients who reported receiving their follow-up care in rural health centers also had significantly lower “Social and Economic” subscores (15.67 ± 3.81) when compared to patients receiving follow-up care in urban health facilities (18.28 ± 4.16), (p < 0.005). Value afforded to family as well as psychological remained high among all groups.

Social and economic benefit was deemed highest amongst those residing in or near urbanized parts of the country, supporting the need to decentralize care to improve access for all—particularly those in more remote areas. Finally, men tended to note more optimistic gains in all areas than women without account for contributing factors. Future directions aim to utilize these results to calculate the cost-effectiveness of cardiac surgery in Rwanda and to support the investment of resources in a sustainable cardiac surgery program that will assist in mitigating the tragic burden of cardiac disease in sub-Saharan Africa.
Identification of a Novel Population of Neurons Involved in Pain Perception

Robert J. Smalley
Harvard Medical School, Francis Weld Peabody Society, Class of 2018

Qiufu Ma, PhD
Department of Cancer Biology, Dana-Farber Cancer Institute

Pain is common, debilitating, and poorly understood. Chronic pain currently affects 100 million Americans, more than cancer, heart disease, and diabetes combined. The attributable economic loss in America is over $500 billion annually. Opiates are effective for treating many forms of pain, but are commonly abused and can cause accidental death. Efforts to develop higher fidelity treatment modalities are hampered by a lack of understanding of the specific roles of various neurons in pain perception.

Anatomically, there are distinct pathways for ascending pain transmission. The spinoparabrachial pathway, which ascends from the spinal cord dorsal horn before synapsing in the parabrachial nucleus (PB) and ascending to the amygdala or hypothalamus, is important for the emotional aspect of pain. The periaqueductal grey (PAG) receives direct projection from the spinal cord and functions as a critical descending pain control center. The subnuclei functions within the PAG and PB are largely unknown.

Using transgenic mice, we identified subsets of neurons with distinct functions and anatomic boundaries through genetic expression using Cre recombinase and in situ hybridization of RNA in several neuropeptides of interest. We then ablate the neurons through viral incorporation of a loxP-flanked transcriptional stop cassette used for conditional activation of a diphtheria toxin receptor (DTR) gene in a Cre-recombinase-dependent manner, expressed only in those cells expressing the previously identified neuropeptides. Following this, behavioral assays are performed on the conditional knockdown mice.

Utilizing the techniques described above, we identified a novel subset of neurons with distinct anatomic boundaries in the Kolliker-Fuse region of the PB in which 95% of neurons expressing Calcitonin Gene-Related Peptide (CGRP) demonstrated co-expression of the TAC1 gene. Other researchers demonstrated these CGRP neurons selectively project to amygdala neurons expressing CGRP receptors, and ablation of PB CGRP neurons does not affect the ability to experience pain, but eliminates the association of pain with concurrent non-noxious stimuli and future avoidance of the non-noxious stimuli.

We are now identifying PAG neurons involved in the control of endogenous analgesic modulation of pain through descending pathways to the locus coeruleus (LC) and rostral ventromedial medulla (RVM). The specific types of neurons in communication with the PAG, their characteristics, and their location in the LC and RVM are unknown.

This better understanding may serve as one step toward the development of novel treatment modalities that lack the side effects of opiate pain management and treat the specific symptoms of a subset of chronic pain patients.
Getting to Zero: Reducing HIV Incidence through Screening, Treatment, and Prevention

William B. Smith
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Harvey J. Makadon, MD
The Fenway Institute

Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS), has been an epidemic since the early 1980s. Today, there are an estimated 1,218,400 persons living with HIV in the United States with 13% of those infected unaware of their infection status. Even though the mortality of AIDS has decreased, the annual incidence of HIV infection remains consistent at an estimated 50,000 new infections per year. Furthermore, minority populations including men who have sex with men, transgender women, black, and Hispanic/latino populations experience disproportionally higher rates of HIV incidence. We developed a self-guided learning module aimed at clinicians, which describes a three-pronged method to reduce HIV incidence based on current literature with an emphasis on screening, treatment, and prevention tactics.

First, since 13% of infected individuals are unaware of their infection status, a universal HIV screening program is essential to identify those that are HIV-positive and prevent the transmission of new HIV infections. Based on recommendations by the USPTF, everyone between the ages of 15-65 should be screened at least once for HIV with a 4th generation immunoassay test. Those demonstrating high-risk behaviors for HIV transmission should be screened at least annually. An effective screening program is a cost-effective tactic to link HIV-positive people to care and reduce the incidence of HIV infection.

Second, we discuss the use of anti-retroviral therapy (ART) regimens as an effective way to prevent the transmission of HIV from HIV-positive people to their uninfected sexual partners. The treatment as prevention study HPTN 052, demonstrated that among serodiscordant couples, adherence to early ART resulted in a reduction of HIV transmission by 96%. This study, among others, demonstrates that treatment as prevention is essential to reducing HIV incidence.

Lastly, we focus on HIV prevention tactics, including risk reduction counseling, condom-use, post-exposure prophylaxis, and pre-exposure prophylaxis (PrEP). PrEP can be particularly effective at reducing HIV incidence among high-risk populations. Though, multiple studies have provided evidence on the efficacy of PrEP among high-risk people, it is largely underutilized in the United States and has great potential to reduce HIV incidence.

This interactive module was developed to educate clinicians on the efficacy of simple efforts they can employ to reduce HIV incidence. In accord with the revised National AIDS Strategy, wider use of these, especially in high-risk minority populations, will improve the efficacy of HIV care and prevention, decreasing the annual incidence of HIV—possibly one day to zero.
Development of a new zebrafish model for studying cell-autonomous connexin mutants linked to atrial fibrillation

Jiunn Song
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Calum A. MacRae, MD, PhD
Division of Cardiovascular Medicine, Brigham and Women’s Hospital;
Harvard Medical School

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia that results in an inconsistent filling of the ventricle during diastole and raises the risk for stroke and heart failure. Several genome-wide association studies (GWAS) have linked multiple genes to AF including connexin 40 (Cx40), a key component of intercellular gap junctions between cardiomyocytes and the primary connexin protein responsible for proper impulse propagation and hence synchronized contraction of the heart. Recently, a nonsense Cx40 mutation (Cx40<sup>Q49X</sup>) was discovered in a human pedigree analysis as a potential cause of familial lone AF. In vitro, Cx40<sup>Q49X</sup> acts as a dominant negative form of both Cx40 and Cx43 by retaining them in the ER and reduces gap-junction plaque formation as well as coupling conductance between neighboring cells. However, the impact of Cx40<sup>Q49X</sup> on impulse propagation in a network of cells has not been studied. Here, we aimed to develop new methods to address the cell-autonomous role of AF-linked mutations via a comprehensive but simple in vivo approach using the zebrafish as a readout model and Cx40<sup>Q49X</sup> as a prime example.

We first designed and cloned gene constructs that contain either the wild-type Cx40 or Cx40<sup>Q49X</sup> sequence, under the control of a cardiac-specific (cmlc2) promoter and in frame with a 3’ fluorophore (dsRed) behind the self-cleaving peptide 2A (P2A) sequence, using the Gateway technology. Placing the dsRed sequence behind this P2A peptide prevents the fluorophore from interrupting the assembly of connexin proteins, while still allowing for identification of the cells expressing the wild-type or mutant Cx40. Restriction enzyme and sequence analysis confirmed the results of successful gene cloning. Similar vectors containing the ubiquitous CMV promoter were generated to study the effect of Cx40<sup>Q49X</sup> in paced immortalized murine atrial HL-1 cells.

Intracellular injection of cmlc2-Cx40-P2A-dsRed constructs into the zebrafish embryos at one-cell stage clearly indicated that scattered dsRed<sup>+</sup> cells could be detected in the heart from 48 hours post-fertilization. Moreover, the dsRed signal did not interfere with the conduction velocity measurements via optical mapping technology. Therefore, we developed a novel strategy to score for the cell-autonomous defects induced by overexpression of AF-linked aberrant proteins in cardiomyocytes. Altogether, these preliminary results pave an exciting new way to use zebrafish as a high-throughput model for studying AF.
Effects of definitive chemoradiation on circulating angiogenic cytokines in head and neck cancer patients

Vishwajith Sridharan
Harvard Medical School, Irving M. London Society, Class of 2018

Jonathan D. Schoenfeld, MD, MPH
Department of Radiation Oncology
Brigham and Women's Hospital

Purpose: Recent studies have suggested a potential synergistic effect between radiation and anti-angiogenic therapy. Although treatment targeting vascular endothelial growth factor (VEGF) is actively being explored in head and neck squamous cell carcinoma (HNSCC), the impact of other complementary angiogenic cytokines that could serve as potential therapeutic targets are unknown. We aimed to prospectively assess changes in circulating VEGF, angiopoietin-1 and -2 (Ang1, Ang2), and placental growth factor (PIGF) that occur during definitive chemo-radiotherapy in HNSCC patients.

Experimental Design: We prospectively collected peripheral blood samples from 24 patients receiving definitive radiation therapy with or without chemotherapy. Serum Ang1, Ang2, VEGF, and PIGF were measured via multiplex cytokine assays, and correlated with disease and treatment characteristics.

Results: The majority of patients had advanced stage, node positive HPV-associated oropharyngeal cancer, and received radiation to a median dose of 70 Gy with concurrent cisplatin. Over the course of treatment, serum VEGF and Ang1 levels decreased in 20/24 (84%, p<0.0001) and 21/24 (88%, p<0.0001) patients respectively, and Ang2 and PIGF levels increased in 20/24 (83%, p<0.0001) patients. Increases in serum Ang2 and PIGF were greatest in node-positive patients (p=0.02). Increases in serum PIGF levels correlated with use of concurrent chemotherapy (p=0.02).

Conclusions: We find significant changes in angiogenic cytokines in the majority of HNSCC patients over the course of chemoradiation that correlate with nodal involvement. Increases in the cytokines Ang2 and PIGF are interesting given their link to tumor associated angiogenesis and poor prognosis. Additional studies are needed to examine the prognostic significance of these markers and explore potential synergies between anti-angiogenic treatments and chemoradiation in HNSCC.
Interviews of Doctors and Nurses Pre- and Post-Deployment to West Africa to Fight the Ebola Outbreak

Kate Carlisle Stoeckle
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

Paul Farmer, MD
Chief Strategist and Co-Founder
Partners in Health

Ebola virus disease (EVD) is a severe and often fatal hemorrhagic fever illness. The current outbreak in West Africa (beginning with the first reported cases in March 2014) is the largest and most complicated Ebola outbreak in history, infecting and claiming more lives than all other outbreaks combined (WHO, 2015). Since March 2014, aid organizations such as Partners in Health (PIH) and Doctors Without Borders have trained and sent more than 700 healthcare workers to West Africa to bolster local control efforts (Ashkenas et al., 2014). Working in an Ebola Treatment Unit (ETU) poses a host of physical and psychological risks to healthcare workers. Furthermore, reentry to host countries bears challenges like quarantine and assimilating amidst public fear and scrutiny.

No academic study to date has gathered oral histories detailing attitudes of health workers on their experiences training for and working in West African ETUs. These individuals are vital not only for their medical expertise but also because they can help build sustainable local healthcare delivery systems that have the potential to keep future outbreaks at bay (Farmer, 2014). We conducted the first qualitative study of PIH-employed clinicians that worked in West Africa to fight the Ebola outbreak. The unique design of this study, in which both before and after interviews were conducted, sheds light on the fears, expectations, and experiences of healthcare workers.

We interviewed 20 PIH clinicians (12 nurses, 8 physicians) pre- and post-deployment: in person within three days of departure, and by phone within two months of return. Interviews lasted between 15 and 40 minutes and were semi-structured. Interviews were transcribed to facilitate analysis. Several themes stood out: (1) many participants described their decision to deploy as being a “gift” to themselves and a moral imperative, rather than an act of martyrdom, (2) many participants expressed profound frustration with the lack of resources available to them in West Africa but ultimately felt that they were able to make a difference in the lives of their patients, (3) after leaving West Africa, several participants arranged Skype sessions with fellow clinicians, from which they derived a deep sense of support and (4) many participants found the interview process itself to be therapeutic. Our study documents areas of concern among PIH clinicians deployed to West Africa and can inform the way we train clinicians for future epidemics.
The Need for Preoperative Baseline Arm Measurement to Accurately Quantify Breast Cancer-related Lymphedema

Fangdi Sun
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Alphonse G. Taghian, MD, PhD
Department of Radiation Oncology
Massachusetts General Hospital

Introduction: Breast cancer-related lymphedema (BCRL) is a highly feared outcome of breast cancer treatment, yet the increasing push for screening and longitudinal monitoring has been hampered by a lack of standardization in quantification criteria. We sought to determine the necessity of preoperative baseline measurement in accounting for temporal changes of upper extremity volume.

Methods: 1028 patients with unilateral breast cancer were prospectively screened for lymphedema with bilateral arm volume measurements by optoelectronic perometry, including a preoperative baseline. Cutoff thresholds were defined as a relative volume change (RVC) of ≥10% for clinically significant lymphedema and ≥5% to include subclinical lymphedema. For the condition of no available baseline, the first postoperative measurement, termed "pseudo-baseline", was substituted in place of true preoperative baseline. BCRL underdiagnosis was defined as RVC ≥5 or 10% with preoperative baseline, when not classified as such with pseudo-baseline; overdiagnosis was defined as the converse. McNemar's test and binomial logistic regression models were used to analyze misdiagnoses of BCRL.

Results: Preoperatively, 28.3% and 2.9% of patients had arm asymmetry between ipsilateral and contralateral arms of magnitude ≥5 and 10% RVC, respectively. Baseline arm volumes were 0.45% higher for the ipsilateral arm and 0.54% higher for the dominant side. In using pseudo-baseline, 41.6% of patients were underdiagnosed and 40.1% were overdiagnosed for ≥5% RVC; this increased to 50.0% and 54.8% at ≥10% RVC. By multivariable analysis, increased pseudo-baseline asymmetry (p<0.0001), increased weight change between baselines (p=0.0169), hormonal therapy (p=0.0085), dominant use of contralateral arm (p=0.0043), and not receiving axillary lymph node dissection (ALND) (p=0.0037) were associated with increased risk of underdiagnosis at ≥5% RVC; not receiving regional lymph node radiation (RLNR) was the only equivalent at ≥10% RVC. Increased pseudo-baseline asymmetry (p=0.0054), not receiving ALND (p=0.0001), and dominant use of ipsilateral arm (p=0.0084) were associated with overdiagnosis at ≥5% RVC; increased pseudo-baseline asymmetry (p=0.020) and not receiving ALND (p<0.0001) were also significant at ≥10% RVC.

Conclusion: Patients absolutely must have a baseline preoperative measurement for accurate quantification of BCRL, which we propose as a minimal requirement for standardization. Factors traditionally associated with decreased risk of lymphedema are also associated with increased risk of misdiagnosis, a critical finding for the design of trials aimed at screening and early treatment of BCRL.
Learning Resource Used Versus Usefulness in the Basic Sciences Curriculum

Monica Tain
Harvard School of Dental Medicine, William Bosworth Castle Society, Class of 2018

Sang Park, DDS, MMSc
Assistant Professor of Restorative Dentistry and Biomaterials Sciences, Associate Dean for Dental Education, Director of Predoctoral Curriculum, Harvard School of Dental Medicine

In accordance with the ADEA Commission on Change and Innovation in Dental Education (CCI) position favoring self-directed and active learning in the dental profession, it is the role of dental schools to instigate such an environment. The present study examines one aspect of the student learning experience by evaluating the use and usefulness of various learning resources during the first-year dental/medical Integrated Human Physiology (IHP) at the Harvard School of Dental Medicine (HSDM) and Harvard Medical School (HMS). Incorporating the more useful resources into class time should be a goal for curriculum development.

The aim of this study is to delineate specific learning resources for the advancement of dental education such that, early on in their training, dental students are provided with the best tools necessary for achieving expertise. This study examines various aspects of using specific learning resources in the first-year Integrated Human Physiology Course (IHP) at HSDM and HMS.

The study population consisted of the dental and medical students of HSDM and HMS, respectively, of the Class of 2018. The IHP course was chosen to examine the use of 29 different learning resources using an anonymous online questionnaire powered by Qualtrics. Cognitive interviews/pilot testing was performed with the Class of 2017 at HSDM/HMS prior to the survey distribution the study population. Questions included frequency of use, form of use, usefulness, and reasons for using or not using a specified resource in addition to final exam grade, gender, and school affiliation. For analysis, the learning resources have been grouped into various categories to discern differential preferences and usefulness among these categories. Limitations of this study include recall bias and differential interpretation of survey questions.

The survey was distributed to one hundred sixty nine students (n=169). Preliminary results indicate that of the four main categories of learning resources analyzed, instructor-guided resources were cited to be used “all the time” by the greatest number of students (42.78%) as compared to online resources (24.44%), student-to-student-interaction resources (5.56%), and resources requiring individual preparation (18.38%). However, the greatest number of students also said that instructor-guided resources were “not at all useful” (11.59%) compared the other stated resources (4.39%, 9.48%, and 10.06%, respectively) and was likewise the lowest cited category of resource for being “very useful”. This suggests that students are not necessarily choosing the most useful resources for them and thus provides the opportunity for an intervention at the level of curriculum development.
Medicine as a lens into the political history of a postcolonial state

Zujaja Tauqeer
Harvard Medical School, Francis Weld Peabody Society, Class of 2018

David Jones, MD, PhD
Harvard Medical School,
Department of Global Health and Social Medicine

The study of politics rarely intertwines with the study of human well-being. Though health and sickness, living and dying are the most intimate and eternal aspects of the human experience, they rarely appear in general history books and political analyses. In the words of historian of medicine Allan Brandt, ‘To overlook the changing material conditions of life, changing age structures, and shifting patterns of births and deaths [is] to neglect the most basic parameters of social institutions and activity.’ In recent decades, the study of history of medicine has added a bold new dimension to the understanding of social beliefs and the structural operation of power in diverse settings ranging from revolutionary France to colonial India to apartheid South Africa.

In this project, I sought to apply analytical tools from history of medicine to understand political developments in Pakistan under military rule in the 1960s. The 60s saw the eruption of military rule in many previously colonized nations, from Nigeria to Burma to the Honduras, often with the support of anti-communist Western governments. While it is well-known that this period established a precedent for military rule in Pakistan and that Pakistan’s interests became firmly wedded to American interests in the region—an alliance that has proved enduring—no effort has been made to understand what these developments have meant for the well-being of Pakistanis.

This study shows how the logic of military rule manifested in medical interventions by studying the trajectory of family planning efforts in the 60s. What was believed to be a strong and active disciplinarian state had in fact ceded sovereignty over its people to international vogues in academia and philanthropy. Decisions about the intimate lives of people and the economic needs of the country were internationalized, derived from economic theories that owed their inspiration to geopolitical alliances and foreign academic trends rather than any systematic understanding of the state of public health needs in Pakistan. Secular, technocratic policies were actually legitimized formulations of political anxieties arising from geographic and political jealousies between nations. In sum, what was heralded as the hopeful birth pangs of a modernist, scientifically-based mode of governance in the developing world was actually an administrative diffusion of charismatic rule by decree in a state which had limited ability to control the populations within its borders.
Evaluating the Health Literacy Environment of Hospitals and Health Centers in Barcelona to Improve the Quality of Care

Jacob T. Taylor
Harvard School of Dental Medicine, Walter Bradford Cannon Society, Class of 2018

Maria Dolores Navarro Rubio, MPH, MSc, MD, PhD
Epidemiology and Public Health
International University of Catalonia

Health literacy is a patient’s level of understanding of basic health information and their ability to make appropriate health decisions based on that knowledge. A health literacy environment (HLE) takes this concept one step further and applies it to the environment of the healthcare setting and how that can affect the healthcare delivery for the patient. The main aim of this project focused on assessing three variables of the HLE in six different hospitals and primary health centers in Barcelona: navigation, print communication, and technology and seeing how these things could be changed to improve healthcare delivery.

To assess these three aspects, a Health Literacy Scan (HLS) was used, which consisted of a series of survey questions that were previously tested and verified. There were five different sections to this survey, two of which were removed because of the lack of resources or time to complete it in its entirety. There were a few questions of the three remaining questions that were removed for various reasons as well, but the rest of the questions were used. Each question (example question “is the information desk sign clear and visible”) of the HLS had a scale of 1-3, 1 correlating to something not done, and 3 correlating to something done well. N/A was also an option. At each hospital or health center, navigation and technology of the entrance, lobby, hallways, etc. and 3-5 departments or units were assessed. Print materials were also gathered to be assessed at a later time. The hospitals will not be compared to each other. Based on the total scores, each hospital will receive a rating and specific feedback for improvement based on the results that were found.

Though the data analysis and results are incomplete, it was found that newer hospitals tended to have higher scores because they were easier to navigate. This generalization may change once the data is fully analyzed. It was also found that public computers and telephones are not applicable at any hospital or health center. The data will be analyzed using excel and if possible, the print materials will be assessed using the Flesch-Szigriszt readability formula. The next few weeks will be spent analyzing the data.

Some limitations of the study include but are not limited to: being a non-native Spanish speaker and the limited amount of questions used in the survey to assess the hospitals.
Creation of a Community Advisory Board for Community-Based Cancer Research in Navajo Nation

Megan Townsend
Harvard Medical School, Francis Weld Peabody, Class of 2018

Sara Selig, MD
Division of Global Health Equity
Brigham and Women's Hospital

American Indians and Alaska Natives (AI/ANs) have the lowest cancer survival rates of any racial group in the United States. Cancer is currently the second leading cause of death among AI/ANs and a leading cause of premature death. Specifically, mortality rates from colorectal cancer are 39% higher in AI/AN individuals as compared to non-Hispanic whites, while death rates from cervical cancers are nearly 50% higher. While some literature exists on Navajo patient perception of cancer screening and advance care planning, very little research exists on the Navajo cancer patient treatment experience, patient preferences, or patient and family perceptions of palliative care.

COPE is a collaborative project between Brigham and Women’s Hospital, Partners In Health, Navajo Area Indian Health Services, and the Navajo Nation Department of Health. In an effort to address disparities in cancer care and cancer outcomes in Navajo Nation, the Community Outreach and Patient Empowerment (COPE) project launched the COPE Cancer Coalition (CCC) in 2012. In order to incorporate a patient-centered approach to CCC programming, we recruited a core group of cancer patients, cancer survivors, and caregivers to serve on a community advisory board.

Community advisory boards are a central component of community-based participatory research methods. These boards typically play integral roles in the development, execution, and analysis of data collected in communities. Our board, called the Patient and Family Advisory Committee (PFAC), was recruited to help the CCC conduct a qualitative study to examine the most important factors influencing cancer care for patients in Navajo Nation.

In the summer of 2015, we recruited 6 PFAC members, developed a curriculum for PFAC members on research methods, and hosted the initial meetings. Our curriculum introduced members to community-based participatory research, qualitative research methods, and interview technique. In the first of two PFAC meetings, members discussed their personal experiences with cancer and obstacles to treatment. In the second meeting, members reviewed a draft interview guide for content, phrasing, and cultural appropriateness. PFAC members practiced interview skills using draft interview guides and brainstormed strategies for patient recruitment for a qualitative study.

In the summer of 2015, we recruited 6 PFAC members, developed a curriculum for PFAC members on research methods, and hosted the initial meetings. Our curriculum introduced members to community-based participatory research, qualitative research methods, and interview technique. In the first of two PFAC meetings, members discussed their personal experiences with cancer and obstacles to treatment. In the second meeting, members reviewed a draft interview guide for content, phrasing, and cultural appropriateness. PFAC members practiced interview skills using draft interview guides and brainstormed strategies for patient recruitment for a qualitative study.

Over the next 6 months, the PFAC will meet monthly to monitor the progress of their qualitative interviews. As data becomes available, we will work with the PFAC to code and analyze interviews. With the results of the qualitative community assessment, we will work with the PFAC to design and implement community-based cancer care interventions.
Understanding the Public’s Perspective on the Integration of Medicine and Dentistry

Hanh T. Tran
Harvard School of Dental Medicine, Walter Bradford Cannon Society, Class of 2018

Christine A. Riedy, PhD, MPH
Department of Oral Health Policy and Epidemiology
Harvard School of Dental Medicine

Dental and medical healthcare currently operate as separate entities and represent fragmentation in the healthcare system. The lack of crosstalk between the two fields has led to a number consequences, such as separation in the pre-doctoral education, delivery of dental and medical care, and differences in insurance systems. The Affordable Care Act recently mandated dental care for children 18 years of age or younger, but has done little to tackle the needs of the adult population, particularly low-income adults, who have fewer stable sources of dental care and are more at risk for oral disease. As a result, disadvantaged adults receive dental treatment in hospital ERs, which is costly and inefficient because ER physicians receive little training in oral health sciences during medical school. Recently, there has been initiative to integrate the delivery of oral and systemic health to improve patient treatment, reduce healthcare costs and reduce disparities in oral care.

While initiatives are leading to integration of medicine and dentistry, there has been limited information collected about the public’s understanding and opinion about integration efforts. The overall goal of this project was to gain an in-depth understanding of the community’s views on integrating medicine and dentistry in two domains – clinical practice and insurance. This was accomplished qualitatively by conducting semi-structured interviews on individuals from the greater Boston area. Individuals were recruited through posted flyers at a public library and academic dental clinic. Additionally, a snowball sampling approach was used to bolster the number of participants. Questions for the semi-structured interview were based on three main areas: general perceptions about oral health and its importance, integration of medicine and dentistry in clinical practice, and integration of medical and dental insurance. Interviews were audio-recorded and transcribed for analysis. A comprehensive content analysis will be used to establish the thematic categories for coding. We will use a mixed method qualitative content analysis, both inductive (conventional approach) and theory-driven approaches for the coding process (directed approach). Codes will be categorized into themes and sub-themes. Quotes will be used to illustrate representative themes/sub-themes.

The final results of this research are pending. To date, 6 individuals were interviewed. While the results of this research are pending, we hope they will reveal the public’s perceptions and opinions about the integration of medicine and dentistry and the impact of the dental-medical divide on the patient population.
Determining Barriers to Maternal and Neonatal Care to Prevent Neonatal Mortality in Eastern Rwanda

Emily Unger
Harvard Medical School, Oliver W. Holmes Society, Class of 2018

Lisa Hirschhorn MD
Department of Global Health and Social Medicine, Harvard Medical School
Brigham and Women's Hospital

Nearly half of the world’s 6.3-million under-five deaths occur in Sub-Saharan Africa, and nearly 40% of them occur within the neonatal period. Since the Genocide in 1994, Rwanda has significantly reduced the under-five mortality rate by focusing on vaccination, nutrition, and clean water initiatives. With these improvements, a rising percentage of under-five mortality is attributable to the neonatal period. To improve neonatal outcomes, it is essential to improve access to obstetrical care. Many of these deaths could be prevented if the barriers to quality health care for pregnant women were removed. To improve care, it is essential to get women’s perspectives about the quality of their care as well as the reported barriers.

In 2013 IMB/PIH started the All Babies Count (ABC) Initiative to “reduce the country’s neonatal death rate through training and mentorship, systems-strengthening initiatives, and quality improvement strategies.” The ABC initiative, a unique comprehensive approach that works at all levels of the health system, is focused on improving quality of care and increasing capacity using evidence-based processes to target antenatal care, delivery services, and postnatal care. In 2013 a baseline study was conducted which aimed to understand women’s satisfaction and access to care. Results from this survey were used to implement QI projects over the next 18 months. In 2015 we conducted an endpoint study to evaluate the impact of the ABC QI Initiatives on mothers’ perceptions of the quality of their obstetrical care as well as their knowledge about when to utilize health services for themselves and their newborns. We trained local data officers, used the same 34-question quantitative survey, determined adequate sample sizes to ensure sufficient power, and trained data entry officers. 559 pregnant and postpartum women from 25 Health Centers in Kayonza and Kirehe Districts in Rwanda were surveyed over the course of 5 weeks. IMB Data Officers are entering and analyzing the data to assess whether the efforts of the ABC initiative have resulted in increased patient satisfaction and knowledge. We plan to do baseline and endpoint comparisons for each health center to look at specific strengths and weakness so that they can learn from one another. If there is no change, they can examine the areas of weakness that still need to be addressed. If there is a positive change, PIH/IMB can extend these QI initiatives within Rwanda and adapt them to other communities to improve quality and access, which saves lives.
Characterization of bone marrow response as a potential biomarker of clinical outcome in patients with glioblastoma

Eugene Vaios
Harvard Medical School, Francis W. Peabody Society, Class of 2018

Brian Nahed, MD, MSC
Department of Neurosurgery
Massachusetts General Hospital

Glioblastoma (GBM) is the most common malignant glioma in adults and carries a poor prognosis. One of the most common adverse effects of chemotherapy with temolozomide (TMZ) is myelosuppression. We hypothesized that the degree of bone-marrow toxicity in patients treated with TMZ correlates with overall survival (OS) and MRI-based time to progression (PFS). Blood counts and other descriptive information were collected retrospectively from 86 patients who had completed at least 6 months of post-chemoradiation TMZ therapy following the Stupp Protocol. By Kaplan-Meier analysis, we report that patients with decreases in platelet counts at 3 months of TMZ had longer PFS (M=681.5d) than patients with increases relative to pre-surgery (M=363.4d), p = .036. Patients with decreases in WBC counts at 4 months and 9 months of TMZ had better OS and PFS, respectively, than patients with increases relative to pre-surgery (M=1078.49d, M=507.33d, p=.001; M=1074.47d, M=486d, p=.01; respectively). Patients with decreases in neutrophil counts at 6 months of TMZ also had longer PFS (M=800.71d) than patients with increases relative to pre-surgery (M=469d), p=.045. At 7 months of TMZ, patients in the top quartile by OS had significantly lower neutrophil counts (M=66.71, SD=9.05) than patients in the bottom quartile (M=80.19, SD=5.49), t(22) = 3.63, p=.002. Higher absolute counts or increases in counts relative to baseline for red blood cell, lymphocyte, basophil, eosinophil, and monocyte counts were associated with significantly better clinical outcomes. If validated, these findings suggest that bone marrow toxicity may be used as a biomarker for clinical outcomes and to guide chemotherapy dosing.
Evidence-based clinical resources in sub-Saharan Africa: Understanding and promoting their usage

Yannis Kalogirou Valtis
Harvard Medical School, Francis W. Peabody Society, Class of 2018

Rebecca Weintraub, MD
Department of Global Health and Social Medicine
Harvard Medical School, Brigham and Women’s Hospital

Health professionals use evidence-based clinical resources (EBCRs) to support clinical decision-making and optimize patient care. In the U.S., use of UpToDate, a popular EBCR, correlates with higher examination scores among residents and lower hospital mortality. Despite its proven effectiveness, introduction of UpToDate and other EBCRs in resource-limited settings (RLS) has lagged, due in part to high subscription costs. In 2009, the Global Health Delivery Project (GHD) launched a partnership with UpToDate to provide free UpToDate subscriptions to qualifying clinicians and institutions in RLS. To study the usage of and demand for EBCRs in RLS, I analyzed usage frequency and patterns among recipients of GHD’s program, and I visited two medical schools (Muhimbili University of Health and Allied Sciences in Tanzania and University of Rwanda in Rwanda) to conduct focus groups and interviews with faculty and medical students to understand their knowledge and attitudes around EBCRs.

My research showed that between 2013 and 2014, 449 individual and institutional GHD UpToDate users logged onto UpToDate approximately 150,000 times and that users from Africa were responsible for 54% of that usage. On average, 184 users (41%) logged in once per week, while 89 users (20%) logged in at least once per day. Topics of interest varied across geographies and might correlate with epidemiological characteristics of the patient population. For example, “Clinical Manifestations of Malaria” was the most viewed topic in Africa, and “Management of Hepatitis B” was the most viewed topic in Asia.

Overall, most medical students in both Tanzania and Rwanda used the Internet regularly and believed that approximately 80% of their colleagues had smartphones with Internet access. Google, Wikipedia, and Medscape were the most widely used online resources among interviewed students. While they had full access to many research journals through the WHO program HINARI, few students knew how to access them. Faculty at both schools used online journals regularly but noted the absence of a reliable, regularly updated source that could be used at the point of care.

My research suggests that there is need and demand for broader access to EBCRs in RLS and that many assumed barriers to EBCR expansion (poor Internet connectivity, lack of training, and lack of familiarity with the Internet) might pose less of a burden than the high cost of EBCRs. Hence, donation programs like GHD UpToDate should be enhanced and expanded to include not only health professionals but also medical students in RLS.
Posttraumatic Stress Disorder in Young Breast Cancer Survivors

Danny A. Vazquez, Jr.
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018
Alexandra J. Miliotis Fellow in Pediatric Oncology

Ann H. Partridge, MD, MPH
Department of Medical Oncology
Dana-Farber Cancer Institute

Posttraumatic stress disorder (PTSD) is associated with morbidity and mortality in affected populations. Cancer survivors experience PTSD at a rate higher than the general population, with young age and female gender identified as risk factors. Given that young women with breast cancer experience greater psychosocial distress following diagnosis, we sought to estimate PTSD prevalence in this population and identify associated risk factors. We hypothesized that the PTSD prevalence would be greater than or equal to that previously reported in the literature (approximately 6%) and that low social support and pre-existing psychiatric comorbidities in particular would be associated with PTSD.

Women diagnosed with Stage I-III breast cancer at age≤40 were surveyed as a part of a multi-site prospective cohort study. Demographic, treatment, psychosocial characteristics (including self-reported psychiatric conditions and use of psychiatric medications prior to diagnosis), anxiety and depression (Hospital Anxiety and Depression Scale), fear of recurrence (Lasry Scale), and social support (Medical Outcomes Study) were assessed within 1 year after diagnosis. PTSD was measured at 30 months post-diagnosis using the PTSD Checklist – Civilian Version (PCL-C); a score ≥ 50 was considered positive for PTSD. Univariable and stepwise multivariable logistic regression were used to evaluate factors associated with PTSD.

572 women were eligible for this analysis; median age at diagnosis was 37 (range: 17-40); 87% had Stage I/II cancer. 37/572 women (6.5%) met criteria for PTSD at 30 months. Lower educational attainment, less financial comfort, less social support, stage 2 (vs. 1) disease, chemotherapy, fear of recurrence, anxiety and depression, and psychiatric comorbidities were associated (p≤0.05) with PTSD in univariable analyses. In multivariable analysis, chemotherapy (OR 3.48, 95% CI=1.09-11.06), anxiety by HADS (OR 20.29, 95% CI=7.83-52.53), and psychiatric comorbidities (OR 4.22, 95% CI=1.40-12.74) were associated with increased likelihood of PTSD; college education (OR 0.25, 95% CI=0.10-0.59) and greater social support (OR 0.41, 95% CI=0.17-0.99) appeared to be protective.

PTSD affects a minority of young breast cancer survivors, with the prevalence in our cohort similar to that seen in other breast cancer populations. Our methods have some limitations. Most data was self-reported and response bias cannot be excluded. Additionally, the PCL-C is a screening tool for PTSD, though is a feasible and validated alternative to the Structured Clinical Interview for DSM-V. Early identification of those at risk for PTSD is essential for the adequate treatment of affected women and for the improvement of health outcomes and quality of life in cancer survivors.
A Retrospective Cohort Study of Medi-Cal’s Reinstatement and Its Effects on Dental Service Utilization

Carolynn T. Vuong
Harvard School of Dental Medicine, Francis Weld Peabody Society, Class of 2018

Yogita B. Thakur, DDS, MS
Ravenswood Family Health Center, East Palo Alto, CA

Nationwide, Medicaid enrollment has reached over 71 million, with 11 million non-elderly, low-income adults receiving coverage under the government insurance program. Medi-Cal, California’s Medicaid plan, is the largest Medicaid program in the United States, covering 11.2 million people, or about 30% of California’s population. Of this population, about 2.2 million were added when Medi-Cal expanded its eligibility requirements in 2013. While many studies have analyzed the utilization of medical services in primary care and hospital services, there is insufficient data on the impact of Medicaid’s re-establishment and the utilization of dental services.

In September of 2013, Medi-Cal reinstated some adult dental benefits, which included routine exams and x-rays. Expanded benefits were added in May of 2014, with restorative procedures such as fillings and full dentures included as well. In San Mateo County of California, Medi-Cal provides coverage to almost 20% of the county’s population.

This study looks at the utilization of dental services over a period of two years (Sept 2012-Sept 2014) that includes no coverage of adult dental benefits under Medi-Cal and its subsequent restoration of coverage for adults in September of 2013. Many studies have looked at the elimination of Medi-Cal dental benefits in 2009, but the more recent re-introduction of these benefits has not been studied. Additionally, most studies on Medicaid and utilization rates involve a more medical-based approach, but this study allows for a dental specific area of study and is unique in that dental services are often treated as an optional area of coverage for health insurances. This analysis allows insight into the association of dental insurance coverage (and lack thereof) with utilization rates of dental services. Analysis of Medi-Cal’s impact on the utilization of regular routine exams versus limited emergency exams and extractions can provide a basis for further study in seeing how different factors, such as age, gender, education level, income level, and insurance status can affect dental care utilization for certain treatments.

Due to delayed data collection, analysis is still underway and results are currently pending.
Defining the Mechanisms of Axon Growth after Limb Amputation

Cameron K. Waites
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Jessica L. Whited, PhD
Brigham Regenerative Medicine Center, Department of Orthopedic Surgery
Brigham and Women's Hospital

In some human amputees, nerve axons grow uncontrollably in the remaining limb stump to form a disorganized mass of nerve tissue, called a neuroma, causing excruciating pain and additional loss of function. The causes of neuroma are unknown, and no preventive therapies are available.

Neuroma formation in humans may result from a latent regenerative program gone awry. An opportunity to address this problem and expand the scope of animal models of limb amputation may be found in the axolotl salamander, an organism in which complete limb regeneration occurs post-amputation, and in which neuroma formation has not been explored. Axolotl limb regeneration depends upon a specialized wound epidermis, the proliferation of tissue progenitor cells of the underlying blastema, and the regrowth of neuronal axons, though the molecular mechanisms are not well understood. Using a wound suture technique analogous to human surgical amputation procedure, full-thickness epidermal skin flaps sutured over the amputated axolotl limb stump prevents successful regeneration.

Based on these observations, we hypothesized that axon growth is intrinsic, such that severed axons regrow to a predetermined length following amputation. We thus used full-thickness skin sutures after amputation to block limb regeneration and then later harvested limb stumps to assay for neuroma. A possible limitation of this approach is that neuroma formation, if it occurs, does so with such low frequency to be logistically difficult for downstream experimentation. However, our initial gross dissection of tissues revealed promising, though unclear, signs of neuroma, and tissues are now prepped for future histological analyses. We also hypothesized that blastema cells in the regenerating axolotl limb secrete factors that promote axonal regeneration. In separate experiments, RNA-seq data obtained from the neuronal cell bodies of regenerating (amputated, non-sutured) limbs and control (non-amputated/non-sutured) limbs were used to construct a de novo transcriptome assembly via Trinity software. Axon outgrowth candidates were identified using EdgeR differential gene expression, analyzed in the literature, and prioritized for future qRT-PCR and/or in situ validation (accounting for RNA expression limitations) and experimentation.

The mechanisms of post-amputation neuroma formation in humans may relate to those of limb regeneration in axolotls. This study is poised not only to answer the unexplored question of axolotl neuroma, but our novel in vivo approach using RNA-seq coupled with a robust axolotl transcriptome may also advance our understanding of neuroma formation in humans and contribute a set of target transcripts whose future experimentation may lead to effective therapeutics.
Developing a novel cortical-to-spinal neural prosthesis for restoring volitional movement in awake-behaving animals

Amy J. Wang
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Ziv Williams, MD
Center for Nervous System Repair, Department of Neurosurgery
Massachusetts General Hospital

Spinal cord injury (SCI) and motor paralysis pose substantial obstacles to daily living. In the context of restoring motor function, it is important to consider that SCI leaves both the cortex and the downstream motor system intact. The cortical areas responsible for encoding important parameters of movement (i.e. limb position, motor intent, and ongoing movement trajectory) remain active following spinal cord injury. An important goal in neuroscience has been to restore volitional motor control to a paralyzed subject’s own limb. Using a primate model, the current study aims to re-route information between the functionally intact brain and downstream muscles, thus developing a novel wireless “neuron-to-neuron” prosthetic approach to motor paralysis.

The primary obstacle to applying this approach has been the lack of understanding of motor system outputs. The efferents associated with corticospinal tracts are not explicitly known, and it is difficult to determine the appropriate combinations of agonistic and antagonistic muscle contractions needed to reproduce specific natural movements. In lieu of this knowledge, we implement an approach that focuses on reaching the intended target of movement rather than recreating the intervening ongoing trajectory.

The current study accomplishes the preliminary and foundational step in the development of the neural prosthetic—namely, estimating motor intent using neuronal recordings. First, the naïve primate is trained to perform a reach-hold task. For each individual trial, a small movable sphere is pseudo-randomly positioned in one of twelve possible locations (four targets per plane, at three different depths). The primate receives a juice reward when he maintains grasp of the ball for 500 ms. Following mastery of the task, an electrocorticography array is placed on the primate’s dorsal pre-motor (PMd) cortex for its role in reach planning and execution. The primate performs the behavioral task once again, and PMd recordings are obtained over 400 trials. We use a population decoding approach to ascertain the target of movement across multiple possible targets in space from anticipatory PMd firings.

The next step will involve implanting electrode arrays in the spinal cord at the level of the brachial plexus and characterizing the full range of arm movements elicited by different stimulation settings. Finally, we will match the decoded PMd signals with specific stimulations to achieve dynamic and multi-targeted movements with the prosthetic in real time. The prosthetic will ultimately be evaluated based on an otherwise functionally paralyzed adult Rhesus macaque’s ability to perform the reach-hold task and to self-feed.
Characteristics of Hospitals Penalized the Most by Federal Pay-for-Performance Programs

David E. Wang
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Ashish K. Jha, MD, MPH
K.T. Li Professor of International Health, Department of Health Policy and Management, Harvard T.H. Chan School of Public Health

The federal government has made significant efforts to shift towards value-based payments for U.S. hospitals by introducing three national pay-for-performance (P4P) schemes: Hospital Value-Based Purchasing (VBP), Hospital Readmission Reduction Program (HRRP), and, more recently, Hospital-Acquired Condition Reduction (HACR) Program. Fiscal year 2015 marks the first time hospitals are eligible to be penalized by all three programs, with Medicare reimbursement rates potentially cut by up to 5.5%. Therefore, we examined which hospitals received the most penalties under all three P4P schemes.

Using publicly available FY 2015 Medicare Final Rule data files, we categorized hospitals into quartiles by P4P penalties received in FY 2015 and defined three groups: most penalized (quartile 4 with highest combined penalty), moderately penalized (quartile 3 and 2), and least penalized (quartile 1). We linked these data to the annual American Hospital Association Annual Survey to identify hospital characteristics. Subsequently, we used multinomial logistic regression analyses to calculate the odds of being the most penalized or moderately penalized versus the being the least penalized by hospital size, teaching status, and safety-net status.

The adjusted odds of being the most penalized for large hospitals was 3.71 [95% CI, 2.23-6.17], major teaching 2.17 [95% CI 1.23-3.83], and safety-net hospitals 1.96 [95% CI 1.46-2.63]. Similarly, large hospitals and safety-net hospitals were generally more likely to be moderately penalized group compared to small hospitals and non-safety-net hospitals. The mean penalty size for the most penalized group was 1.86% compared to 0.56% for moderately penalized. The least penalized group received a bonus of 0.47%.

Large, major-teaching, and safety-net hospitals were far more likely to be penalized the most by all three P4P programs. As the intent of these programs is to penalize low value healthcare, the current message from federal policymakers suggests that quality of care is worse at these types of hospital compared to small, non-teaching hospitals. Whether this is true is unclear. However, these findings, which represent the full breadth of P4P for U.S. hospitals, raise important concerns about adequate risk-adjustment and whether hospitals are being penalized for taking care of socioeconomically vulnerable or medically complex patients.
Defining the Role of IL-33 Producers in Skeletal Muscle Repair and Disease

Kathy K. Wang
Harvard Medical School, Irving M. London Society, Class of 2018

Diane Mathis, Ph.D.
Division of Immunology, Department of Microbiology and Immunobiology
Harvard Medical School

Skeletal muscle has a remarkable capacity for regeneration after injury. This regeneration is driven by activation and differentiation of muscle stem cells, known as satellite cells, which fuse to form new myofibers. However, in diseased states and in aged muscle, regeneration is impaired and skeletal muscle is replaced by fatty and fibrous tissue, which interferes with contractile function.

A distinct population of regulatory T cells (Tregs) that accumulates in injured skeletal muscle has been found to control inflammation and enhance satellite cell differentiation to limit fibrosis. These skeletal muscle Tregs display high levels of the receptor for IL-33, a recently characterized alarmin of the IL-1 family that is released during necrotic cell death. IL-33 has emerged as an important cytokine that is engaged in regulating the immune response following muscle injury. However, the identity and function of IL-33-producing cells in skeletal muscle have not been defined.

Here, we used immunofluorescence and flow cytometry to identify markers of IL-33 producers in murine skeletal muscle. We found that IL-33 producers are stromal cells that express a set of markers (CD45-, CD31-, Sca1+, PDGFRα+, gp38+) consistent with their being fibro/adipocyte progenitors (FAPs) and fibroblastic reticular cells (FRCs). These IL-33 producers were found in close apposition to peripheral nerves and around muscle spindles, which sense stretch and communicate positional information to the central nervous system, enabling proprioception. Thus, IL-33 producers may play a role in mediating communication between the nervous system and the immune response.

To probe the interactions between peripheral nerves and IL-33 producers, we are assessing changes in IL-33 production and Treg accumulation in injured muscle after denervation and in two mouse models (Bace1 and Egr3 knockouts) that exhibit impaired formation of muscle spindles. To obtain an unbiased view of signaling pathways and neuro-immune interactions that are mediated by IL-33 producers, we will perform RNA-seq analysis on IL-33 producers that have been sorted from skeletal muscle, fat, colon, lymph node, and spleen.

Given that there are currently no adequate treatments for muscular dystrophies, and that impaired wound healing is problematic in aging and diabetes, better understanding of the role of the IL-33-producing stromal cell population may open new avenues for developing therapeutics to improve muscle regeneration and limit destructive fibrosis and fatty accumulation in disease.
Accuracy of and Compliance with Established Risk Stratification Guidelines for Febrile Neutropenia in the Emergency Department

Thomas Wang
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

Christopher Baugh, MD, MBA
Director of Operations, Emergency Department
Brigham and Women's Hospital

Multiple established guidelines exist for risk stratifying and treatment for oncology patients with febrile neutropenia (FN). The most well-known risk stratification tool is the Multinational Association for Supportive Care in Cancer (MASCC) score. Low-risk patients are candidates for oral antibiotics and outpatient management, but the pattern of treatment for low-risk patients in an emergency department setting is unknown. We hypothesized, from clinical observation, that patients with FN are overly admitted and aimed to review the treatment process to observe its alignment with established guidelines.

We conducted a structured chart review of cancer patients with febrile neutropenia presenting to an urban, tertiary-care teaching hospital affiliated with a leading cancer center between January 2010 and December 2014. We queried a research database to find all patients seen in the emergency department with an absolute neutrophil count <1000 during the study period, and then reviewed visit notes to find patients diagnosed with febrile neutropenia of unknown etiology at the index visit. We retrospectively determined the patient’s MASCC score and correlated this score with treatment delivered, site of subsequent care, two other risk stratification guidelines provided by the American Society of Clinical Oncology (ASCO) and Infectious Diseases Society of America (IDSA), and clinically significant outcomes.

We found a total of 173 eligible visits. The mean MASCC score was 21, with 66% of patients deemed “low-risk” (score ≥21). If the ASCO and IDSA guidelines were applied, 62% of patients in the “low-risk” group had at least one clinical indication justifying inpatient admission. Overall, 96% of patients in the low-risk MASCC score group were admitted, including 88% of patients with zero clinical criteria for admission. Clinical outcomes when comparing low and high risk patients respectively were 7.0% vs. 10.3% for positive blood culture (OR 1.5; 95% CI 0.5-4.7), 1.7% vs. 17.2% for sepsis (OR 11.8; 95% CI 2.5-55.8), and 0.9% vs 10.3% for death within 30 days (OR 13.2; 95% CI 1.5-112.1).

At this single center, low-risk patients were frequently hospitalized and treated with intravenous antibiotics despite eligibility for alternative outpatient management. In this vulnerable population where avoidable hospitalization is highly important, strategies to increase compliance with management guidelines should be explored. Nevertheless, we are limited by the retrospective nature of the study, along with its relatively small cohort based at a single center. Further research will need to be conducted to evaluate the study’s generalizability to other institutions.
Diabetes presents an increasing burden globally as a leading cause of disability and cardiovascular diseases. To prevent the complications of diabetes, patient retention and quality care, including adherence to guidelines by clinicians, is critical. This project explored the documentation of key patient information and the care provided by the Non-Communicable Diseases (NCD) program at Inshuti Mu Buzima health care facilities between June 2012 and June 2015. The current standards of diabetes care have been adapted from the “PIH Guide to Chronic Care Integration for Endemic Non-Communicable Diseases-Rwanda Edition”.

Providers document care delivered into a paper record and this is then transferred into the electronic medical record system (EMR), which has been adapted in all NCD clinics. We reviewed EMR data to measure: (1) completeness of baseline demographic and clinical history information important for patient follow-up and care, and (2) rates of documented delivery of recommended care. Descriptive statistics was used to describe the level of documentation of all measures.

We found that documentation of patients’ address was excellent with only 1% missing, but about one quarter of patients had missing information for other demographic and clinical history information including marriage status (27%), occupation (28%), HIV status (25%), smoking status (22%), and alcohol use (25%). Phone number was largely missing (75%).

Rates of documented receipt of recommended care varied at intake and on follow-up care. There were good levels of documentation of basic routine measures including blood pressure, pulse, and weight at both intake and follow-up visits. Documentation of delivery of less frequent routine measures like creatinine, HbA1c, proteinuria, and monofilament testing were much lower. Foot examination for ulcers was well documented at intake (76%), but very poor for follow-up visits (1%). Documentation of blood sugar was low at intake (only 41%) and completely absent at follow-up (0%).

There were a number of limitations to our approach. As this data was retrieved from EMR, the care documented may not be a true reflection of the care provided in the clinic. There are many factors that could contribute to the level of documentation seen. These include: (1) gap in care delivery, (2) a gap in documentation in paper charts, and (3) gap in EMR documentation. From observations and interactions with the team, it is likely a combination of all factors at play. The next steps will be to identify the cause of these observed results, and subsequently implement necessary quality improvement initiatives.
Assessment of Teamwork Attitudes among Interdisciplinary Healthcare Team Members in the Program of All-Inclusive Care for the Elderly (PACE) Model

Chloe Wong
Harvard School of Dental Medicine, William Bosworth Castle Society, Class of 2018

Lisa Thompson, DMD
Advanced Graduate Education Program in Geriatric Dentistry
Harvard School of Dental Medicine

The geriatric population in the United States is expanding. It is estimated that by 2030, persons 65 years and older will represent 19% of the population. Given the trend in population aging, there has been heightened emphasis on multidisciplinary care models to contain healthcare costs, respond to complicated health conditions, and increase the efficiency of healthcare delivery. One such approach is the Program of All-Inclusive Care for the Elderly (PACE), a government-funded, team-based, multidisciplinary model that offers patient-centered care to eligible patients ages 55 and older with chronic care needs while maintaining their independence in their home.

Interprofessional communication and teamwork are especially important in geriatric care where patients experience complex health issues and are vulnerable to adverse effects across the care continuum. Teamwork behaviors are integral in any setting where health professionals interact on behalf of shared goals for patient care. These behaviors reduce gaps through care coordination, shared problem-solving and shared decision making.

The aim for this pilot study was to assess the self-reported teamwork attitudes among healthcare team members in a PACE site. We hypothesize that healthcare team members at PACE sites will have positive attitudes towards aspects related to team structure, leadership, situation monitoring, mutual support, and communication. To test our hypothesis, we distributed the TeamSTEPPS™ Teamwork Attitudes Questionnaire (T-TAQ) to healthcare team members of two Element Care PACE sites in Lynn, Massachusetts via Qualtrics, an online survey platform. Healthcare team members include physicians, nurses, physical therapists, social workers, behavioral health specialists, oral health providers, administrators, support staff, and other employees involved in patient care.

The results are still pending. T-TAQ scores will be compared to evaluate potential similarities or differences in teamwork attitudes. Results will be stratified by select demographic data and will be used to assess team structure, leadership, situation monitoring, mutual support, and communication. We hope this study will provide baseline data to inform further studies and interventions to improve health care, access, and delivery for the geriatric population in a multidisciplinary setting.

Limitations for this study include limited sample size and generalizability, sample bias, and non-responder bias. This area deserves a more systematic study with a larger sample size and random assignment to further understand teamwork attitudes in an interdisciplinary primary care setting.
Role of MicroRNA-181b in Regulating Hydrogen Peroxide Signaling in Endothelial Cells

Danny Wong
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Mark W. Feinberg, MD
Department of Medicine, Cardiovascular Division
Brigham and Women’s Hospital

Acute myocardial infarctions are the leading cause of death in the United States and most other industrialized countries. Following these events, reactive oxygen species produced in the ischemic regions of the heart contribute to inflammation, fibrosis, and remodeling. In particular, hydrogen peroxide (H₂O₂) has been shown to mediate endothelial cell apoptosis, growth, and proliferation through such protein kinases as Erk, p38, and JNK.

MicroRNAs – single-stranded RNA molecules that regulate gene expression through either repressing translation or promoting mRNA degradation – have important roles in endothelial cell activation, vascular inflammation, and immune cell differentiation, among other processes. Specifically, our lab has previously demonstrated that miR-181b inhibits NF-κB-mediated endothelial cell activation and vascular inflammation and protects against chronic inflammation in the context of atherosclerosis.

In this study, we investigated the effects of miR-181b on H₂O₂-mediated signaling pathways in endothelial cells in order to better understand the role of miR-181b in oxidative stress and acute myocardial infarction.

RNA and protein were harvested from human umbilical vein endothelial cells (HUVECs) that were (i) treated with H₂O₂ or (ii) transfected with miR-181b or non-specific mimics prior to treatment with H₂O₂. RNA and protein extracts were analyzed using quantitative-PCRs and western blots, respectively. Preliminary data show that H₂O₂ treatment may decrease miR-181b levels, and that miR-181b overexpression may repress H₂O₂-induced levels of phosphorylated JNK2 but not phosphorylated Erk, p38, JNK1, or IκBα. In addition, miR-181b overexpression may reduce H₂O₂-induced expression of PAI-1, a marker of cardiovascular risk.

Current experiments aim to determine the effects of miR-181b on H₂O₂-induced changes in (i) expression of pro-inflammatory proteins (e.g. COX-2, E-selectin); (ii) expression of apoptotic markers (e.g. annexin V, caspase-3); and (iii) cell proliferation. Mechanistic experiments will also be conducted to elucidate how H₂O₂ reduces miR-181b levels and how miR-181b influences levels of phosphorylated JNK2.

Taken altogether, our results indicate that miR-181b may play a role in regulating reactive oxygen species signaling in endothelial cells. Further studies are needed to understand the relationship between miR-181b and H₂O₂ and to determine whether miR-181b can inhibit oxidative stress responses in an in vivo model of acute myocardial infarction.
Expression of FOXJ1 and the Ciliogenesis Gene Program in Glioblastoma

Michael P. Wu
Harvard Medical School, Irving M. London Society, Class of 2018

Sandro Santagata, MD, PhD
Division of Neuropathology, Department of Pathology
Brigham and Women’s Hospital

Glioblastomas (GBM) are deadly, incurable brain tumors that are thought to be driven by subpopulations of glioma cancer stem cells. These cancer stem cells are not only important for tumor initiation, but also produce tumor heterogeneity and are largely resistant to treatment. Despite their significance in GBM tumorigenesis, the nature of these cancer stem cells is not well understood. Glioma stem cells may aberrantly utilize transcriptional programs that are normally expressed by neural stem cells during the processes of normal neurodevelopment and regeneration.

By performing immunohistochemical staining on primary GBM tumors, we have identified a subpopulation of cells within GBM tumors that expresses the transcription factor FOXJ1, a master regulator of motile ciliogenesis. Interestingly, FOXJ1 is also required for the development of neural stem cell populations that line the ventricles of the brain. Therefore, we hypothesized that expression of FOXJ1 in GBM may contribute to the cancer stem cell niche. When grown in tumor neurosphere culture, a subset of GBM tumor cells retains expression of FOXJ1. We analyzed microarray gene expression data of several primary GBM cancer cell lines and found that FOXJ1 expression was correlated with the expression of genes involved in motile cilia production. This ciliogenesis gene program is known to be activated in multiciliated cells. However, there have been no reports of multiciliated tumor cells in GBM. Our preliminary results suggest that there may be aberrant, dysfunctional expression of the ciliogenesis gene program within a subpopulation of GBM tumor cells, which has potential implications for cell cycle progression and cell signal sensing.
The Role of Intermittent Hypoxia in the Pathogenesis of Non-Alcoholic Fatty Liver Disease

Winona W. Wu
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Raymond T. Chung, MD
Division of Gastroenterology
Massachusetts General Hospital

Non-alcoholic fatty liver disease (NAFLD) is a condition that is characterized by the accumulation of fat in the liver without the driving force of alcohol or hepatitis. Found in 25-46% of Americans, NAFLD has emerged as an epidemic condition that is predicted to become the primary cause of chronic liver disease in the U.S. In particular, a notable subset of affected individuals may additionally present with active inflammation and develop non-alcoholic steatohepatitis (NASH), a progressive form of NAFLD that often not only leads to liver damage and cirrhosis, but also will likely become the most common indication for liver transplantation by 2020.

Despite the complications that NASH poses to human health, the risk factors associated with the development of NASH, as opposed to simple steatosis (SS), are not well characterized. Interestingly, recent investigations have discovered that obstructive sleep apnea (OSA), a disease characterized by intermittent drops in oxygen levels while sleeping, may induce profound hypoxemia in the liver and increase the risk of inflammation and fibrosis in NAFLD. However, the mechanisms by which OSA contribute to the development of hepatic injury are unknown.

To elucidate the relationship between OSA and NASH, we performed in vivo and in vitro studies to examine the influence of intermittent hypoxia (IH) on the hepatic microenvironment. We isolated sera from healthy controls, patients with NASH/OSA, and patients with SS/no OSA and subjected them to a Luminex bead-based multiplex assay to measure serum levels of the pro-inflammatory cytokine IL-6, which has been associated with NASH. In doing so, we discovered that patients with OSA/NASH exhibited greater IL-6 secretion levels than those with no OSA/SS and controls. In addition, we exposed hepatocyte and macrophage cell lines to conditions of normoxia (21% oxygen), chronic hypoxia (1% oxygen), and intermittent hypoxia (20 minutes of 1% oxygen, 40 minutes of 21% oxygen) for six hours, and assessed alterations in inflammatory markers. We found that hepatocytes demonstrate a significant induction in IL-6 under conditions of IH, and discovered that this upregulation may be dependent on antioxidant response element (ARE) activation. We also demonstrated that macrophages observe similar IL-6 induction under conditions of IH, and polarize towards a pro-inflammatory M1 phenotype.

These results suggest that IH may contribute to NASH pathogenesis by promoting a pro-inflammatory state in the hepatic microenvironment. Future studies will seek to elucidate pathways leading to ARE/IL-6 induction, understand the mechanisms of M1 polarization, and assess methods of reversing the M1 phenotype to further comprehend the connection between OSA and NASH.
Corticosteroid Injections for Adhesive Capsulitis: A Review

Ryan C. Xiao
Harvard Medical School, Walter Bradford Castle Society, Class of 2018

Arun J. Ramappa, MD
Chief of Sports Medicine and Shoulder Surgery, Department of Orthopaedics
Beth Israel Deaconess Medical Center

Adhesive capsulitis is a self-limiting condition in a majority of patients and is often treated non-operatively. However, symptoms may take 2-3 years to resolve fully. A small, but significant, portion of patients requires surgical intervention. Conservative treatment of adhesive capsulitis may involve one, or more, injections of corticosteroid. The purpose of this systematic review was to evaluate the efficacy of corticosteroid injections for the treatment of adhesive capsulitis.

A review of articles indexed by the United States National Library of Medicine was conducted by querying the PubMed database for studies involving participants with adhesive capsulitis, frozen shoulder, stiff shoulder, or painful shoulder. Articles that included corticosteroids, glucocorticoids, steroids, and injections were included. Additional references were reviewed from the bibliographies of the retrieved articles. Expert opinion and review articles were excluded. Studies without control or comparison groups were excluded. Studies comparing corticosteroid injections to operative procedures were excluded. Comparisons to physical therapy were included as physical therapy or home exercises often accompanies corticosteroid injections as standard of care. Using this review strategy (Figure 1.), 16 studies met the inclusion criteria.

Data items extracted from each study included: study design, study population, intervention, single or multiple injections, location of injections, injection mixture, control population, follow-up duration, and outcome measurements.

The data indicate that corticosteroid injections provide significant symptom relief for 2 to 24 weeks. Injections can be performed intra-articularly or into the subacromial space. Evidence suggests that a 20mg dose of triamcinolone may be as effective as a 40mg injection. It remains unclear whether image-guided injections produce a clinically significant difference in outcomes when compared to landmark-guided (blind) injections. Corticosteroids may be less beneficial for diabetic patients. Patients using protease inhibitors (anti-retroviral therapy) should not receive triamcinolone because the drug-drug interaction may result in iatrogenic Cushing’s syndrome.

Corticosteroid injections for adhesive capsulitis demonstrate short-term efficacy, but may not provide a long-term benefit. More high-quality, prospective studies are needed to determine whether corticosteroid injections using ultrasound-guidance significantly improve outcomes.
Application of Whole Exome Sequencing to the Genetic Diagnosis of Limb-Girdle Muscle Weakness

Liwen Xu
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Daniel MacArthur, PhD
Analytic and Translational Genetics Unit
Massachusetts General Hospital

Limb-girdle muscular dystrophies (LGMDs) are a heterogeneous group of rare muscle disorders in which progressive skeletal muscle weakness and wasting affect primarily the shoulders, hips and proximal limbs. At least 22 genes are causally linked to LGMDs; and others are implicated in metabolic, congenital and other myopathies that can present with LGMD-like patterns of muscle weakness. For patients affected by myopathies characterized by limb-girdle weakness (LGW), receiving a genetic diagnosis can impact their prognosis, therapeutic options and reproductive choices. Recently, traditional methods for diagnosis based on candidate gene sequencing have been supplanted by whole exome sequencing (WES), which provides a comprehensive search across all genes for the most compelling causal variant, unbiased by clinical ascertainment. We hypothesized that WES analysis can effectively prioritize causal variants of LGMDs and clinically similar myopathies.

Here, we studied 262 patients—249 isolated probands and 9 families—of mixed ancestry referred to 15 clinical centers throughout Europe. All fit our inclusion criteria of unexplained LGW. After WES was performed and processed, we identified single nucleotide variants (SNVs), short insertions and deletions by joint calling across all samples, including 60,706 reference samples from the Exome Aggregation Consortium (ExAC). The final call-set was analyzed using the xBrowse platform. We focused on known muscle disease genes, and prioritized variants that 1) were rare in databases such as ExAC and 1000 Genomes; 2) impacted protein sequence or proximal splice sites; and 3) segregated with the disease phenotype within families.

Likely causal variants were identified in 86 families (33%) and involved 35 genes. These included known causal genes of the most prevalent subtypes of autosomal recessive LGMD2 (CAPN3, DYSF, SGCA, FKRP, TTN and ANO5) and autosomal dominant LGMD1 (LMNA and CAV3). Three patients were homozygous for pathogenic variants in DOK7, GFPT1 and RAPSN—genes implicated in congenital myasthenic syndromes characterized by limb-girdle and axial distribution of weakness. Two other patients were compound heterozygous for pathogenic changes in GAA, which causes glycogen storage disease II (Pompe disease) with a similar clinical course to that of LGMDs. These latter four genes represent diagnoses with effective therapies available, all of which are currently being applied.

Our results demonstrate that WES represents a powerful approach to diagnosis in a clinically and genetically heterogeneous disease, and in a subset of patients can identify diagnoses that alter clinical outcomes. In subsequent work we will extend this study to the discovery of novel genes for LGW.
Yield of CT Pulmonary Angiography in the Emergency Department when Providers Override Evidence-Based Clinical Decision Support

Zihao Yan
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Ramin Khorasani, MD, MPH
Vice Chair, Department of Radiology
Director, Center for Evidence Based Imaging
Brigham and Women’s Hospital

Use of advanced medical imaging in the emergency department (ED) has increased substantially. Of particular interest is the ED use of CT pulmonary angiography (CTPA) for patients with suspected pulmonary embolism (PE). Clinical decision support (CDS) integrated with a computerized physician order entry (CPOE) system is capable of improving workflow efficiency, and increasing guideline adherence. Determine the frequency of, and yield after, provider overrides of evidence-based clinical decision support (CDS) for ordering CT pulmonary angiography (CTPA) in the emergency department (ED). Typically, CDS implementations do not include “hard stop” interventions except for the most serious circumstances. Therefore, physicians often override CDS recommendations, usually without providing any clinical justification. In one study, providers overrode 95% of repeat CT CDS alerts. It is not known if this exercise of clinical judgment in overriding CDS is warranted.

This Institutional Review Board-approved study was performed at a tertiary-care, academic medical center ED with approximately 60,000 annual visits and included all patients with suspected pulmonary embolism (PE) undergoing CTPA between 1/1/2011-8/31/2013. Each CTPA order was exposed to CDS based on the Wells Criteria. For patients with Wells Score (WS) ≤4, CDS alerts suggested D-dimer testing, as acute PE is highly unlikely in these patients if D-dimer levels are normal. We compared CTPA yield when providers overrode CDS alerts (by obtaining CTPAs in patients with WS ≤4 and normal--or no--D-dimer testing) to orders adherent to Wells criteria (CTPAs only in patients with WS >4 or WS ≤4 with elevated D-dimer). A validated natural language processing tool identified positive PE diagnoses, with subsegmental/indeterminate diagnoses removed by chart review. We used Chi square and Student’s t-tests for statistical analysis.

Of the total 2,993 CTPAs, 589/2,993 (19.7%) did not adhere to the evidence-based CDS. Among 2993 CTPA orders, 563 had WS ≤4 but no D-dimer testing; 26 had WS ≤4 and normal D-dimer. CTPA yield in this override group was 4.2% (25/589; none with a normal D-Dimer), compared to 11.2% (270/2404) in the adherent group (p <0.001).

In conclusion, CTPA yield for acute PE in the ED was 2.7-fold lower when providers ignored CDS alerts compared to when providers adhered to evidence embedded in CDS. Our findings suggest that stronger interventions may be needed to further reduce the nearly 20% of CTPA requests that override education-only CDS alerts, primarily by ignoring D-dimer testing in “PE unlikely” patients. Further studies are needed to determine what subset of this patient population would benefit from D-dimer test, which if normal, would obviate the need for CTPA. Education-only CDS interventions, even if based on validated decision rules, are unlikely to optimize evidence-based decision making if providers can simply ignore CDS alerts and proceed with imaging.
Market Analysis: Orthopedic Medical Device FDA 510(k) vs. PMA Approval Feasibility

Brian W. Yang
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2018

Charles S. Day, MD, MBA
Hand & Upper Extremity Surgery, Department of Orthopedics
Beth Israel Deaconess Medical Center

The Food and Drug Administration (FDA) is responsible for regulating and overseeing medical devices sold in the United States. Currently, devices can be approved through either the premarket approval (PMA) process, which requires clinical trials, or through the less-rigorous 510(k) premarket notification route, which exempts devices from clinical trials if they prove to be substantially equivalent to an existing device.

For the past decade, there has been growing concern in the medical literature and public sphere regarding the efficacy of these FDA approval processes. Devices approved through the 510(k) route have been shown to result in increased recalls and greater risk to patients, particularly in orthopedics. With the recent increase in publicized device recalls, calls for stricter and overhauled device clearance policies have been made. Adequate information is needed to inform the design of any changes in these clearance processes. However, while previous studies have assessed the costs associated with the PMA and 510(k) approval processes, no study to our knowledge has addressed the economic feasibility of approving various devices through these two routes.

Using cost, revenue, and market size data, we created a statistical model to estimate the time needed to recoup 510(k) and PMA investment costs for a representative collection of orthopedic medical devices, categorized by anatomical location and procedure type. While large-market orthopedic devices such as hip implants and knee implants could expect to recoup the PMA investment costs relatively quickly (1.01 years and 0.65 years, respectively), many small-market devices, including radial plate systems (22.25 years), reverse shoulder replacements (15.87 years), and anterior cervical spacers (6.68 years) would take significantly longer. After factoring in FDA approval time, six out of the thirteen medical device systems analyzed would take over 7 years to recoup their concept-to-market investment costs through the PMA. Only the radial plate system would take over 7 years to recoup investment costs through the 510(k) route.

Although the 510(k) process has demonstrated safety concerns, broad requirements for PMA approval may be too financially unreasonable. Adequate information is needed to inform schemes for new frameworks. This study could help FDA policymakers decide how to efficiently alter device clearance policies to ensure both safety and foster innovation.
A Storybook Approach to Oral Health Education in Primary School Children

Leigh Varborough
Harvard School of Dental Medicine, Francis Weld Peabody Society, Class of 2018

Cynthia Pine, BDS, PhD, MBA, FDSRCS, CBE, FCGI
Department of Dental Public Health, Institute of Dentistry
Barts and The London School of Medicine and Dentistry

Dental caries is a highly prevalent disease in children and is preventable. Though many advances in dentistry have helped to prevent childhood dental caries, caries continue to increase globally at an alarming rate. New preventative techniques at the public health level should be studied and implemented to lower the rate of caries occurrence. One such technique may be the use of storybooks for oral health education. The purpose of this study was to determine if dental health, diet, and behavior change techniques are an important part of what children recall after hearing a story with embedded oral health messages for the first time. Should this be an important component of participant recall, this and similar storybooks could be used as an educational tool for children at home and in school to improve oral health.

This research was carried out in 3 schools in London, England with 24 participants aged 5-6 in their first year of primary school. At each of the 3 schools, 2 focus groups with 4 participants in each group were interviewed. One focus group at each school was read a test book with embedded dental health, diet, and behavior change messages. The other focus group at each school was read a similar control book with but with no embedded health messages. Free recall questions were use in the beginning of the focus group followed by prompted recall questions. Transcripts of the focus groups were analyzed using a qualitative content analysis approach.

The content of the storybook was largely remembered by free recall of the participants. In each of the 3 test groups, the topic of brushing teeth before bed was mentioned as free recall without prompting. Participants in all 6 test and control groups recalled that a sandwich was eaten in the story. The concept that they had eaten a healthy lunch was mentioned by 2 of the 3 test groups as free recall. The participants had a more difficult time recalling what the contents of the healthy lunch. The participants in the test groups recalled a small amount of the embedded behavioral change techniques including 2 of the 3 test groups recalling Dad helping the characters brush their teeth and 2 of the 3 test groups recalling Dad giving the characters a sticker after brushing their teeth. These results support a storybook approach as an effective oral educational tool for this age group.
Developing Effective Communication Strategy for Global Oral Health Interest Group

Hannah Yoo
Harvard School of Dental Medicine, Walter Bradford Cannon Society, Class of 2018

Brittany Seymour, DDS, MPH
Harvard School of Dental Medicine
Department of Global Oral Health

Oral and dental conditions and diseases are among the most prevalent health problems in the world. Dental decay in adults and children, oral lesions of HIV/AIDS, periodontal diseases, craniofacial developmental defects, and oropharyngeal/salivary gland neoplasms occur largely unchecked, notably but not exclusively in underserved communities and resource-poor nations. Furthermore, it is expected that the incidence of dental caries will increase in developing countries as a result of growing consumption of sugar. As a result of the rapidly growing incidence of dental caries and other oral diseases and the World Health Organization’s Oral Health report and Consortium of Universities for Global Health Global Oral Health Interest Group recently developed ‘Global Oral Health Competencies’. These competencies are presented as a first step toward integrating the global oral health workforce into the mainstream of health workforce discussions and trends and expanding oral health competencies for both oral and non-oral health professionals.

Prior to the start of the project, there was no overarching global communication framework for oral health providers, researchers, or students. Thus, there was a need to develop an effective communication strategy that would allow members of the International Association of Dental Research, World Health Organization, Consortium of Universities for Global Health Global Oral Health Interest group, and oral health providers, researchers, and students to network and understand the ‘Global Oral Health Competencies’ outlined by the Consortium of Universities for Global Health. This summer I worked to:

1) Conduct a systematic literature review and individual interviews with GOHIG members and populate the GOHIG website with purposefully curated resources and materials supporting the GOHIG-designed global oral health competencies

2) Develop an empirical communication framework which will include email list serve communications, website development, and social media platforms

In May, I attended the annual CUGH Global Health Conference and participated in the GOHIG 2015/16 annual planning session luncheon. At this conference, I interviewed oral health leaders and professors from across the country to understand the current needs of the global oral health community. In addition, I conducted a systematic literature review to understand current global health issues and oral health competencies. This literature review informed the design of an anonymous survey sent to the GOHIG membership. The survey reached out to 30 members of the GOHIG and asked for information regarding current needs of oral health community and understanding of oral health competencies.

Subsequently, this data was used to create a website and twitter account to publicize the CUGH mission and oral health competencies. Based on feedback from the conference, luncheon, survey, and interviews, we developed a communication framework targeted primarily at the GOHIG and wider CUGH membership and accessible to the global public. This website has been curated with resources regarding oral health competencies and current global oral health research.

The website and communication strategy is the beginning of a streamlined communication hub and best practices for uniting the profession across the globe, educating non-dental professionals, and working toward global oral health improvement. Moving forward, we are creating a blog that will serve as a platform for future global oral health initiatives. Regular social media and email communications are planned. The GOHIG communication strategy is managed by the GOHIG director in collaboration with the CUGH internal communications and IT teams.
An investigation of skin biopsy outcomes for evaluation of acute-onset erythematous nodules in immunocompromised children

Grace J. Young
Harvard Medical School, Walter Bradford Cannon Society, Class of 2018

Minnelly Luu, MD
Department of Dermatology
Children’s Hospital Los Angeles

Among immunocompromised pediatric populations, the presence of dermatologic red nodules can be potentially indicative of life-threatening infections. These nodules generally present as atypical due to the immunocompromised state of the patient, rendering difficulty in efficient and accurate clinical identification. Acute eruptions of red nodules in these populations may carry a broad differential diagnosis, including fungal, bacterial, and atypical mycobacterial infections as well as inflammatory disorders and drug reactions.

Notably, a rapid diagnosis and subsequent treatment is often critical to ensure a successful prognostic outcome in these patients, although there is a paucity of literature with regards to the diagnostic yields of skin biopsies in immunocompromised pediatric populations. In lieu of this, our study proposes a retrospective review analysis of the diagnostic outcomes of biopsies and tissue cultures performed on immunocompromised children presenting with new-onset red nodules at a pediatric tertiary care hospital. Analysis will aim to assess diagnostic yields of biopsies taken, impact on subsequent therapy, prognostic outcomes, and the role and value of biopsy in immunocompromised pediatric patients.

The dermatopathology reporting database at Keck School of Medicine of USC was queried for inpatient pediatric cases from CHLA from 2010-2015. Clinical descriptions from biopsy reports with terms “erythematous,” “violaceous,” “nodule,” “papule,” “neutropenic,” and “immunocompromised” were identified, with subsequent review to confirm inclusion criteria. 46 patients were selected. Of this cohort, the predominant gender was male, with various mediators (including CBC, etc.) mediating the overall progress of infectious vs. infectious disease. Given the schematic interplay between the immune system, the skin as an organ, and the presentation of nodular disease, this case series—the first of its kind—provides a better view into the socio and physical dynamics when treating pediatric immunocompromised patients with potential skin lesions.

The primary outcome variable of biopsy diagnosis, results are to be calculated in terms of percentage of the overall denominator. Impact on subsequent therapy as well as prognostic outcomes will be calculated as percentages and means. Results are anticipated to provide a framework for diagnostic yields of skin lesions in immunocompromised pediatric inpatients as well as clinical and laboratory predictors of infectious versus non-infectious outcomes

The study is limited by nature of being retrospective, in terms of both quantitative and qualitative constraints on the data and variables collected. An additional limitation involves the socioeconomic topography of the study site, which is situated in a predominantly low-SES, Spanish-speaking neighborhood. As a result, a large proportion of patients treated at the site are self-identified as Hispanic, which may have implications on study generalizability.
Pain Management among Dominican Patients with Advanced Arthritis: A Qualitative Study

Amy Yu
Harvard Medical School, Francis Weld Peabody Society, Class of 2018
Rheumatology Research Foundation Medical Student Preceptorship

Jeffrey N. Katz, MD, MSc
Orthopedic and Arthritis Center for Outcomes Research
Brigham & Women’s Hospital, Harvard Medical School

Advanced arthritis and total joint replacement (TJR) recovery are painful experiences and often prompt opioid use in developed countries. Physicians participating in the philanthropic medical mission Operation Walk Boston (OpWalk) to the Dominican Republic have observed that Dominican patients require substantially less opioid medication following TJR than US patients. We conducted a qualitative study to investigate approaches to pain management and expectations for postoperative recovery in patients with advanced arthritis undergoing TJR in the Dominican Republic.

We interviewed 20 patients before TJR during OpWalk 2015 using a moderator’s guide with open-ended topics including pain self-care and care seeking behaviors, and expectations for postsurgical pain and recovery. Interviews were conducted in Spanish, audiotaped, and transcribed verbatim into Spanish and English by a translation company. English transcripts were analyzed using content analysis by two investigators. The Cohen’s κ was 0.86 (95% confidence interval 0.80 – 0.92), suggesting “excellent” inter-rater reliability.

Patients discussed a range of pharmacologic and non-pharmacologic approaches to pain management, from traditional Western medications to prayer and relaxation. They reported modest use of pain medications and limited knowledge of opioids, and most relied on non-pharmacologic therapies and family support to cope with pain. Patients held strong religious beliefs that offered them strength to cope with chronic arthritis pain and prepare for acute pain following surgery. Patients exhibited a great deal of trust in powerful others, expecting God and doctors to cure their pain through surgery.

Several limitations of the study should be noted. The sample size was comprised of OpWalk Boston patients, who represent a small sample of the individuals in the Dominican Republic with arthritis pain who actively sought pain relief through TJR. Furthermore, interviews were performed within a span of four days, limiting our capacity to incorporate accumulating knowledge to our interview protocol as data were collected.

Our findings note the importance of incorporating individual coping mechanisms into pain management strategies. Health care providers should be encouraged to gain a thorough understanding of a patient’s pain coping behaviors and identify strategies to support those mechanisms when appropriate. This is especially important for clinicians working with patients in the developing world as well as minority patients in the developed world. Such an approach has the potential to reduce the burden of chronic arthritis pain while limiting reliance on opioids, particularly for patients who do not traditionally utilize powerful analgesics.
Dental Curricula, CODA, and Patients with Special Needs: Where Are We Now?

Golmah Zarinkhou
Harvard Medical School, William Bosworth Castle Society, Class of 2018

Steven P. Perlman, DDS, MScD, DHL (hon)
Clinical Professor of Pediatric Dentistry
Boston University Goldman School of Dental Medicine

Providing oral healthcare for patients with special needs (PWSN) is difficult for many reasons including the behavioral challenges, need for longer appointment times/special training/equipment, and low reimbursement. The Commission on Dental Accreditation (CODA) 2004, mandates, “Graduates must be competent in assessing the treatment needs of patients with special needs.” Regardless, there are no standards for didactic training, nor are there requirements for students to complete treatment or provide direct clinical care for PWSN, merely a note that the potential patient pool “may include” such patients. A 1999 survey of American and Canadian dental schools found that 53% of schools provided fewer than 5 hours of didactic time dedicated to care for PWSN, and 73% of schools dedicated less than 5% of actual clinical instruction time. Since then and after CODA in 2004, there have been efforts to survey dental schools and students about their knowledge, attitudes, didactic instruction and clinical training. Students with clinical training to complement didactic coursework have more confidence, competence, and willingness to see PWSN once in practice. However, it is not known whether there is continuously increasing positive attitudes towards treating PWSN, if the willingness has plateaued, or if it has shifted into specialty areas such as pediatric dentistry.

The specific aims of this project are to survey pre-doctoral students' perceptions of treating PWSN. We expect to find a significant relationship between positive attitudes towards providing oral health care for PWSN and didactic/clinical time in pre-doctoral programs.

Students from Southern California dental schools differing in amount of time/focus treating PWSN will be surveyed about their knowledge/attitudes in treating PWSN, and we have distributed surveys to one such school to date. We acknowledge there may be some halo effect or bias in student responses, given that students may have volunteered to provide dental treatment to athletes during the 2015 Special Olympics World Summer Games.

Once the data collection phase of this project is completed, descriptive (frequency, means, median) along with nonparametric (Chi square, Wilcoxon) statistics will be used to determine the relationships between didactic/clinical time and students’ attitudes towards treating PWSN.
Predicting Isocitrate Dehydrogenase Mutation Status and Survival Outcome in High-Grade Gliomas with Multimodality Imaging Markers

Biqi Zhang
Harvard Medical School, Francis Weld Peabody Society, Class of 2018

Patrick Y. Wen, MD
Department of Neurology, Brigham and Women’s Hospital; Center of Neuro-Oncology, Dana-Farber Cancer Institute

Glioblastoma multiforme is the highest-grade glioma with a median survival of 12 to 15 months following the best available therapies. Tumors with mutations in the isocitrate dehydrogenase (IDH) gene family, however, confer longer overall survival relative to their wild-type counterparts. Since IDH mutation consistently co-occurs with highly abnormal vasculature and a hypermethylated phenotype, both promising therapeutic targets, accurately determining IDH status in GBM tumors may have both prognostic and diagnostic value. Unfortunately, the most commonly used method for detecting IDH mutation status is histologic analysis, which detects only one IDH mutation. Since investigators have discovered that genetic alterations within glioma manifest as quantifiable changes in magnetic resonance imaging (MRI), the goals of the present study are to identify, optimize, and validate imaging biomarkers that can be implemented clinically to predict genetic status and survival outcomes.

We hypothesized that a multiparametric model with conventional and advanced imaging markers will accurately predict IDH mutation status, overall survival, and progression free survival in high-grade gliomas. To test this hypothesis, we retrospectively examined pre-operative MRI studies of 91 patients with either histologically confirmed World Health Organization grade III glioma or grade IV glioblastoma of IDH mutant and wild-type status. We will extract imaging features from pre-contrast T1-weighted (T1W), T2W, Apparent Diffusion Coefficient (ADC) map, and post-contrast T1W sequences. Patients will be randomly assigned to either the training cohort or the validation cohort, after which the combined imaging features will be optimized via our machine-learning algorithm to predict IDH status and survival outcome with the training cohort. Given IDH mutation and clinical data obtained from patient medical records, the Kaplan-Meier method will be used to evaluate genetic and survival predictions.
Characterizing a novel small molecule inhibitor of HIV-1 Env-mediated entry, PF-68742

Connie Zhao
Harvard Medical School, Irving M. London Society, Class of 2018

Joseph Sodroski, BS MD
Department of Cancer Immunology & Virology
Dana-Farber Cancer Institute

HIV/AIDS continues to pose a serious global health challenge, for which a safe, effective, and accessible prophylaxis has yet to be found. The HIV-1 envelope glycoproteins (Env) that mediate virus entry represent attractive targets for novel approaches to prevent the establishment of infection. During entry, Env undergoes conformational changes triggered by binding to the receptors, CD4 and CCR5. Small molecules present immense potential to not only contribute to a prophylaxis that is specific to HIV-1 and potent against a broad range of strains, but also serve as structural probes of Env conformations on the entry pathway. The identification and characterization of novel small-molecule entry inhibitors may bypass limitations demonstrated by existing compounds, improve prophylactic potency and breadth while reducing viral escape, and inform further strategic inhibitor development by expanding our understanding of entry.

We hypothesized that the recently identified HIV-1 entry inhibitor PF-68742 might represent a novel class whose mechanism involves binding to an unknown Env conformational intermediate. To begin characterizing this mechanism, we used cell-cell fusion and single-round viral entry assays to assess the effects of PF-68742 and existing entry inhibitors on the function of wild-type (WT) and mutant Envs from a variety of HIV-1 strains.

While baseline susceptibility to PF-68742 varied considerably amongst WT Envs in a profile distinct from that of existing inhibitors, it did not differ significantly amongst mutants with varied Env reactivity or global inhibitor sensitivity. Moreover, similar to CD4 mimetics but unlike all other entry inhibitors, PF-68742 was able to enhance CD4-independent entry with a strain susceptibility profile inversely related to that of inhibition. Together these results suggest a possible mechanism of PF-68742’s antiviral activity. Similar to CD4 mimetics, PF-68742 may promote a conformational change crucial to entry that results in the formation of a short-lived activated intermediate, transiently enabling entry in the absence of attachment to the CD4 receptor but ultimately decaying to an inactivated state. The addition of CD4 mimetics did not impede enhancement, suggesting that PF-68742 likely targets a unique binding site, conformational intermediate, and/or conformational change from that of CD4 mimetics and other inhibitors.

Moving forwards, HIV-1 Env sequence alignment may reveal more about the mechanism by identifying viral determinants of interstrain variability in sensitivity. We hope to characterize the binding site and specific conformational change promoted by PF-68742. Beyond mechanistic characterization, future work will be needed to improve the breadth and potency of PF-68742 for potential clinical application.
Year 3
Abstracts
Emergency Department-Based Needs Assessment from a Safety Net Hospital in South Los Angeles

Melanie F. Molina
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2017

Medell Briggs-Malonson, MD, MPH, MSHS
Medical Director of Quality, Martin Luther King, Jr. Community Hospital
Assistant Clinical Professor, David Geffen School of Medicine

South Los Angeles (L.A.) is one of the most socioeconomically disadvantaged and medically underserved regions in Los Angeles, California. The community consists of approximately 1.35 million people (72% Latino, 22% African-American) and has the worst health outcomes in L.A. County due to the lack of primary and specialty healthcare services within the community. In May 2015, a new, private, non-profit hospital, Martin Luther King, Jr. Community Hospital (MLKCH), opened in South L.A. to address the community’s health care needs. To do so, MLKCH is piloting an innovative, multidisciplinary care coordination model to ensure patients receive timely medical treatments, health education, and safe care transitions within the hospital and back to the outpatient setting. This model is also being used in the emergency department (ED) since it is the first point of contact for many members of the community with the health care system. The ED model focuses specifically on the coordination of various medical and social services before the patient is discharged.

The objective of this study is to conduct an ED-based patient needs assessment to evaluate patients’ perspectives on the accessibility and quality of healthcare within their community. The aims of the assessment are to 1) identify patient-perceived obstacles that prevent regular access and receipt of primary and specialty community-based health care, 2) assess patient awareness of and perceptions regarding community-based social services in South Los Angeles, and 3) evaluate patient-, community- and systems-level factors that can be targeted through ED-based interventions to improve coordination of care that lead to improved health outcomes.

We conducted semi-structured interviews in English and Spanish with a convenience sample of 32 patients that presented to the MLKCH ED. Each interview was recorded and transcribed. Transcripts will be analyzed for common themes using grounded theory methods. The final interview themes will be used to inform the further development of the ED-based care coordination model.

The main limitation of the study is the sampling method. A convenience sample of ED patients was selected based on the inability to randomize patients that met the study criteria. Therefore, the data obtained may not represent all of the perspectives from the South L.A. community. We attempted to counter this bias by sampling patients from each ED shift, and we will compare the final study patient demographics to those of the community.
Title: Systemic Delivery of Opsins to Cochlear Nucleus Neurons Using Adeno-Associated Virus

Sumi Sinha
Harvard Medical School, Walter B. Cannon Society, Class of 2017
Howard Hughes Medical Institute Medical Fellow

Daniel J. Lee, MD
Pediatric Otology and Neurotology, Department of Otolaryngology
Massachusetts Eye and Ear Infirmary

Background: Despite recent advances in auditory brainstem implant (ABI) technology, user experiences vary widely and have not reached the same potential as cochlear implant patients. An optogenetic-based ABI, using light instead of electrical stimulation, would reduce electrical spread and non-specific activation of the cochlear nucleus (CN) to potentially decrease undesired side effects and increase specificity of ABIs. Previous work from our group demonstrated that the CN neurons can be photosensitized by viral-mediated gene delivery of opsins, such as ChR2 or Chronos. This approach involves local introduction of viral vector and opsin. Local vector delivery, however, necessitates an invasive surgical craniotomy approach and in human direct access to the CN for local injection would be limited. Here we assess the effectiveness of systemic injection to deliver opsins to the CN in a murine model as an alternative to direct injection. CN photosensitization via injection into the superficial temporal vein or tail vein would move the model closer to a translatable optically based ABI.

Methods: CBA/CaJ mice at age P2 were injected with adeno-associated viral vector (AAV) serotype 2/9 carrying a CAG promoter for the GFP or Chronos-GFP coupled gene into the superficial temporal vein. Control mice were either injected with saline or received no injection. After 6-14 weeks of recovery, AAV2/9-CAG-GFP mice underwent transcardiac perfusion with 4% PFA and extracted brains were cryoprotected in 30% sucrose for two days. Samples were then frozen in Tissue-Tek OCT compound, sectioned, and mounted onto slides for histological evaluation. Slides were stained for GFP expression along with nuclear marker DAPI and neuronal marker NeuN. GFP expression was evaluated using confocal microscopy.

Results: Compared to no injection, AAV2/9-CAG-GFP showed GFP expression in the cerebellum, which confirmed effective transfection as demonstrated in previous studies. GFP expression was also found within the CN, demonstrating the ability to transfect the CN using viral delivery. Mice injected with AAV2/9-CAG-Chronos-GFP showed GFP expression co-localizing with NeuN staining, suggesting effective transfection of neurons within the CN.

Conclusions: The histological expression of GFP in the CN after injection of vector into the superficial temporal vein shows that it is possible to use a viral mediated systematic approach. This work will further be evaluated with physiological testing to determine whether gene transfer of Chronos into CN neurons will be associated with light-evoked responses as measured in upstream auditory centers, moving closer to a translatable optogenetic-based ABI.
Characterization of the Propofol-Induced Frontal Encephalogram in Autism Spectrum Disorder (ASD)

Elisa C. Walsh
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

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction and restricted, repetitive patterns of behavior, interests, and activities. ASD affected nearly 1 in 88 children in 2012, and the prevalence continues to rise. The underlying pathophysiology remains poorly understood. However, research into the pathogenesis of ASD has sharply accelerated in the past several years. Recent evidence suggests that deficits in neuronal proliferation, differentiation, migration, and synapse formation in utero may lead to aberrant functional and structural connectivity in individuals with ASD.

During propofol-induced unconsciousness, frontal encephalogram (EEG) demonstrates (a) large-amplitude slow-delta oscillations (0.1-4Hz) and (b) frontally coherent alpha oscillations (8-13Hz). Preliminary results from our laboratory indicate significant age-related changes in the propofol-induced EEG power spectra and coherence. Strikingly, total EEG power increases from 0-6 years old, peaks at 6 years, and declines with increasing age until age 21. This is thought to correlate with the trajectory of neurodevelopment, with myelination and synapse formation followed by synaptic pruning. Given the proposed deficits of connectivity in ASD, we hypothesized that the propofol-induced frontal EEG in ASD patients would show significant changes in power and coherence compared to age-matched developmentally normal children.

We recorded 4-channel EEG data using the SEDLine (Masimo, Irvine, CA) monitor during the routine care of ASD patients between 3 to 27 years of age (mean±SD, 12.01±6.40) receiving propofol as a primary anesthetic (n=29). We used the DSM-5 definition of ASD, encompassing autism, Asperger’s, and pervasive developmental disorder (PDD). We excluded patients with epilepsy, known neurological malformations, and systemic syndromes. For each patient, we analyzed the EEG using multitaper spectral and coherence analysis, with coherence estimated between frontal channels F7 and F8.

Preliminary data review suggests reduced slow-delta band coherence in teenaged (age 11-19) patients with ASD relative to age-matched controls. Final data analysis is pending acquisition of a sufficient number (n=40) of ASD patients. At this point, we will divide patients into age subgroups and define age-matched control groups from our database of pediatric patients. Average power will be calculated from the EEG spectra 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 will then compare the power and coherence as a function of age in ASD vs. control patients. We will also collaborate with pediatricians to assign a severity rating to each ASD patient for further analysis.
Year 4
Abstracts
Evaluation of CT Imaging Features of Non-Small Cell Lung Cancer During Chemoradiation

Vishesh Agrawal
Harvard Medical School, Irving M. London Society, Class of 2016

Raymond H. Mak, MD
Department of Radiation Oncology
Brigham and Women’s Hospital, Dana Farber Cancer Institute

Lung cancer is the most common cause of cancer related deaths in the United States, representing 13.5% of new cancer cases and 27.2% of all cancer deaths. Unlike other malignancies, there are few tumor markers that are correlated with non-small cell lung cancer (NSCLC) progression or treatment. Prior studies have demonstrated the use of NSCLC tumor imaging at various stages of treatment to predict clinical outcomes. These studies have typically used single dimensional features or single time point imaging to assess tumor burden. Based on such literature, we anticipated that we could develop better models to predict clinical outcomes using advanced quantitative imaging features.

In this study, patients with Stage IIA-IIIB NSCLC treated with chemoradiation followed by resection were assessed. CT features including volume, diameter, and texture were quantified using imaging obtained during the course of therapy. Univariate and multivariate logistic regression were used to determine association with clinical endpoints including pathologic complete response (pCR), overall survival, progression-free survival, and locoregional recurrence-free survival.

Using this data, we demonstrated multiple CT based associations for tumor response to chemotherapy and radiation therapy that were improvements on existing tumor response models. Our data showed that tumor volumetric features captured during treatment can be used as an early predictor of pathologic response. Tumors with greater percentage volume change (OR 1.06 [1.02-1.09], p=0.002) and diameter change (OR 1.04 [1.01-1.06], p=0.006), independent of tumor size, had better response to therapy and decreased local recurrence. Additionally, we identified seven tumor texture features prior to therapy that were associated with histopathologic response to chemoradiation. We believe these texture features are correlated to tumor heterogeneity and density and thus may reflect tumor cellular burden.

Quantitative CT imaging may thus provide greater clinical information about tumor response to therapy than absolute tumor sizes or conventional response assessment models. We believe that the development of such imaging based models can provide additional information regarding the efficacy of cancer therapies.
Quality of Life in Children with Cutaneous Stigmata of Tuberous Sclerosis Complex

Cary S. Crall
Harvard Medical School, Francis Weld Peabody Society, Class of 2016

Jennifer T. Huang MD
Dermatology Program, Boston Children’s Hospital

Tuberous sclerosis complex (TSC) is a genetic condition of variable phenotype characterized by development of hamartomas in multiple organ systems. Nearly all patients with TSC have one or more of the skin lesions characteristic of the disorder including angiofibromas (AF). AF are most commonly located on the face and have the potential to cause disfigurement. In spite of this, Quality of Life (QoL) has not been studied in TSC patients and their caregivers.

Topical rapamycin is a novel and effective treatment modality for AF in patients with TSC. However, in our experience, many patients do not have access to topical rapamycin due to lack of insurance coverage and prohibitively high costs of treatment.

We hypothesized that presence of untreated AF was negatively associated with patient and caregiver QoL in patients with TSC. We also hypothesized that access to topical rapamycin was low in patients who would benefit from this treatment. To test these hypotheses, we conducted a cross-sectional cohort study to investigate QoL of TSC patients with facial AF and their caregivers. Patients with TSC seen at BCH and their caregivers were asked to fill out standardized QoL measurement tools including the CDLQI, CADIS, and Skindex-Teen as well as a questionnaire related to access to care.

We found that caregivers of patients with AF had significantly poorer QoL scores compared to caregivers of those without AF, as measured by a modified CADIS questionnaire (31.7 [CI 28.83, 34.56] vs. 11.71 [CI -1.84, 25.27], p=0.0035). We also found that among TSC patients with AF, those who received AF treatment had a significantly better QoL score compared with those without treatment, as measured by the CDLQI (mean 3.83 [CI 2.59-5.06] vs. 9.50 [CI 4.63-14.37], p=0.0010).

In regard to access issues, 41.2% of patients surveyed had never received treatment for their skin condition. Among those whom had topical rapamycin recommended as a treatment option 32.3% never able to get this medication covered by insurance.

In conclusion, we found that presence and lack of treatment of AF significantly impacts QoL in TSC patients and their caregivers. While effective therapies are available, prescribers should be aware of access barriers, including lack of insurance coverage, prohibitively high costs, and supply issues. Future prospective studies are needed to investigate the impact of skin-directed therapy on QoL in TSC patients and their caregivers.
Fifty Years of Health Spending by Low, Middle, and High-Income Americans and Implications in the Era of Increased Cost Sharing

Samuel Dickman
Harvard Medical School, William Bosworth Castle Society, Class of 2016

Danny McCormick, MD, MPH
Department of Medicine
Cambridge Hospital

U.S. medical spending growth has slowed since 2004, coincident with increased cost-sharing, which might particularly discourage lower-income persons from seeking care. We examined health expenditure trends for each income quintile using individual-level data (n=659,725) from 22 nationally representative surveys conducted between 1963 and 2012. In 1963, the poorest quintile had the lowest expenditures, despite having the worst health status. By 1977 their expenditures exceeded those for other Americans, a pattern that persisted until 2004. Between 2004 and 2012, expenditures fell 3.7% for the poorest quintile, while rising 12.5% for the middle-three quintiles and 19.7% for the wealthiest, which now has the highest expenditures. The post-2004 divergence in health expenditures across income groups was limited to the under-65 population. We conclude that the slowdown in health expenditure growth in the non-elderly has been driven primarily by lower spending among the poorest segment of the US population.
Patients with systemic cancer have lower ovarian reserve and require higher gonadotropin doses for fertility preservation

Andrey V. Dolinko
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2016

Elizabeth S. Ginsburg, MD
Department of Obstetrics and Gynecology
Center for Infertility and Reproductive Surgery
Brigham and Women’s Hospital

BACKGROUND: Available therapies to treat malignancies are often gonadotoxic and impair fertility. Improved 5-year survival rates among women of reproductive age diagnosed with cancer means that more women may be facing the prospect of infertility. Fertility preservation (FP) treatments now exist, but it is unclear whether the presence of cancer has a detrimental impact on ovarian reserve or the results of ovarian stimulation (OS).

OBJECTIVE: To evaluate OS outcomes in women with systemic or local cancer.

METHODS: Retrospective cohort study of patients undergoing OS from June 2007 to October 2014. The responses of cancer patients to their 1st OS cycle for FP (n=147) were compared to patients with no cancer (NC) undergoing IVF/ICSI for male factor infertility (n=664). Cancer diagnoses were defined as local (LC, stage I-III solid malignancy, n=105) or systemic (SC, hematologic or stage IV solid malignancy, n=42). Multivariable linear, Poisson, and logistic regressions were applied to calculate β-coefficients, relative rates, and odds ratios, respectively, and 2-sided Wald p-values (p).

RESULTS: Women with SC were significantly younger than women with NC or LC. Adjusting for age and BMI, women with SC had significantly lower baseline antral follicle count than women with NC or LC. They also required significantly higher doses of FSH than women with NC or LC. Women with SC had significantly greater odds of having a cycle cancellation as compared to women with NC (OR=14.4) or LC (OR=17.0). No significant differences were observed among the three groups regarding duration of stimulation, number of oocytes and mature oocytes retrieved, or number of embryos created. Fifteen women returned to use their frozen embryos; eight transfers resulted in live births for a 44% live birth rate per cryopreservation transfer cycle. One patient returned to use her frozen oocytes, but did not achieve pregnancy. To date, 19 of the 147 cancer patients have died; 1 of these had a live birth via gestational carrier prior to death.

CONCLUSIONS: These data suggest that women with cancer have lower ovarian reserve and require higher gonadotropin doses to obtain similar oocyte and embryo yields compared to women with infertile male partners. Those with SC are at greater risk of cycle cancellation, suggesting decreased ovarian reserve. Current findings may provide valuable information to providers for more appropriate counseling of patients of child-bearing age diagnosed with malignancies about the efficacy of FP therapies.
The Cultural Elements Underlining the Community Health Representative – Client Relationship in Navajo Nation

Vikas Gampa
Harvard Medical School, William Bosworth Castle Society, Class of 2016

Sonya Shin, MD, MPH
Division of Infectious Diseases, Department of Medicine
Brigham and Women's Hospital

The Navajo Nation Community Health Representatives (CHR) are trained community health workers who provide crucial services for patients and families, including basic health education and in-home health assessments. The success of the CHRs’ interventions depends on the interactions between the CHRs and their clients. We sought to understand the culturally specific factors that affect the CHR-patient interaction.

We conducted in-depth interviews with 16 CHRs from December 2014 to April 2015. Interviews were transcribed and coded according to relevant themes. Final codes were agreed upon and double-coded by 3 Navajo and non-Navajo team members. Code summaries were organized into a narrative using grounded theory techniques.

We identified four main findings. Trust is fundamental to a well-functioning CHR-client relationship. The ability to build and maintain trust is defined by tradition and culture. Accordingly, CHRs must be respectful of the diverse traditional and social practices of their clients. Finally, the passing of clients brings together the CHR, the client’s family, and the community through spiritual and traditional practices.

Understanding the cultural elements of the CHR-client relationship will allow the Navajo Nation CHR program to train and help CHRs in building trusting relationships. Additionally, such knowledge will inform the work of community partners and other indigenous communities working to strengthen CHR programs.
Optical Coherence Tomography for Noninvasive Imaging of the True Vocal Fold

Jordan Garcia
Harvard Medical School, Francis Weld Peabody Society, Class of 2016

Christopher Hartnick, MD, MS
Department of Otolaryngology,
Massachusetts Eye and Ear Infirmary

Optical coherence tomography is a promising technology to noninvasively assess vocal fold microanatomy and may be helpful in guiding the treatment of pediatric vocal fold disorders. The goal of this study was to use optical coherence tomography to study normal vocal fold development, characterize common pediatric vocal fold lesions, and understand how the components of vocal fold tissue are reflected in optical coherence tomography images. In vivo imaging of pediatric patients undergoing anesthesia will be imaged using a special optical coherence tomography probe and ex vivo experiments will be undertaken to understand the presence of collagen, the most common extracellular matrix protein found in vocal fold tissue, alters optical coherence tomography imaging. Images collected from both in vivo and ex vivo studies will be analyzed using ImageJ software and relative attenuation coefficients and mean pixel intensities will be extracted for analysis for in vivo and ex vivo studies, respectively. The results of this study will both enrich our understanding on normal vocal fold development, the structure of common pediatric vocal fold lesions, and help achieve a deeper appreciation of what optical coherence tomography images of vocal fold tissue represents. With these results, optical coherence tomography may be further developed into a tool that can guide management for pediatric vocal fold disorders.
Diagnostic success and prediction of tumor subtype of renal mass biopsy improves with experience: longitudinal results in a single series cohort of 1233 tumors

David Kuppermann
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2016

Adam S. Feldman, MD, MPH
Department of Urology
Massachusetts General Hospital

The role for percutaneous renal mass biopsy (RMB) remains controversial with utilization patterns varying significantly between institutions. Concerns about non-diagnostic rates and a limited ability to determine tumor subtype and grade may have prevented the widespread adoption of RMB. We describe RMB patterns in a large single institution cohort including diagnostic rates and predictors of diagnostic success.

A retrospective review was performed within our institutional database of RMBs conducted at Massachusetts General Hospital from 1998 to 2012. We assessed trends in diagnostic rates and ability to distinguish renal cell carcinoma (RCC) histologic subtype and grade annually and per chronologic quintile. Biopsies were deemed diagnostic if definitive histopathologic diagnosis was reported, whether benign or malignant. Diagnostic success and discrimination of subtype and grade were separately assessed by multivariable logistic regression adjusting for size and type of lesion (solid vs. cystic).

A total 1233 biopsies were performed on 1169 patients. Mean tumor size was 3.2 cm (SD=1.97) and 83% were solid. Overall diagnostic rate was 78%. A total of 693 (56%) biopsies diagnosed RCC, 142 (12%) oncocytoma/oncocytic neoplasm, 65 (5%) angiomyolipoma, 19 (2%) metastases, 48 (4%) other. We noted a trend toward improved diagnostic rate annually (OR: 1.07; p<0.001) and per quintile (OR: 1.17; p=0.001). Discrimination of RCC subtype also improved annually (OR: 1.15; p<0.0001). Tumor grade was reported in 242 (35%) of RCC biopsies with no observed temporal trend. A total of 274 patients had surgery for RCC on biopsy, 98% of which were concordant with surgical pathology. On multivariate logistic regression, increasing year of biopsy was independently associated with diagnostic rate (OR: 1.05; p=0.025) and subtype discrimination (OR: 1.15; p<0.0001). Other predictors of diagnostic rate on multivariate analysis were solid lesion (OR: 12.09; p<0.0001) and size >1.5cm (OR: 2.32; p<0.0001).

Diagnostic success of renal mass biopsy improves with experience. RMB offers an ability to dependably identify a tissue diagnosis, determine RCC subtype, and help guide clinical decision-making for small renal masses.
Creation and Validation of a Brief Surgical Procedure Code List for Outcomes Research in Resource-Limited Settings

Charles Liu
Harvard Medical School, Walter Bradford Cannon Society, Class of 2016
HMS Traveling Fellowship, Academic Year 2014-2015

Paul G. Firth, MBChB
Department of Anesthesiology
Massachusetts General Hospital

Conditions amenable to surgery represent a significant portion of the burden of disease worldwide, accounting for 10% of deaths and 14% of disability-adjusted life years lost. Today, however, over five billion people worldwide lack access to safe, timely, and affordable surgical care, and the outcomes experienced by surgical patients are least understood in low- and middle-income countries (LMICs).

An important barrier to improving access to and quality of surgical care in resource-poor settings is the dearth of reliable data, due in part to the lack of a standardized system for classifying surgical procedures. The applicability of existing procedure coding systems in LMIC hospital settings is limited by their size, complexity, and cost of implementation. The coding of surgical procedures has been a particular challenge in Uganda and at Mbarara Regional Referral Hospital (MRRH), a 323-bed hospital and one of the country’s busiest surgical centers. A brief procedure code list could improve data collection for administrative, quality improvement, and research purposes at MRRH and in other resource-limited settings.

Here, we describe the development and validation of an abbreviated surgical procedure code list at MRRH. We reviewed operating room logbooks to identify all surgical operations performed between January 1 and December 31, 2014. Based on the documented indication for surgery and procedure(s) performed, we assigned each operation up to four procedure codes from the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), Volume 3. These codes were aggregated to generate procedure code lists. Each surgical procedure was assigned codes by one of two investigators working independently, and a random 20% of procedures were assigned codes by both investigators. The Kappa statistic representing inter-rater reliability in assignment of codes was 0.7037.

During the one-year study period, 6464 surgical procedures were performed at MRRH, to which we assigned 7623 total and 438 unique procedure codes. 113 procedure codes represented 90% of codes assigned, 183 represented 95%, and 281 represented 98%. These constituted short, intermediate-sized, and long code lists, respectively.

Finally, to validate these procedure code lists, we assessed the ability of the intermediate-sized (95%) code list to describe surgical procedures performed at MRRH during the two-month validation period of August 1 to September 30, 2015. We hypothesized that our procedure code list would describe ≥90% of surgical procedures performed at MRRH during this time period. We found that our list described ___% of procedures performed during the two-month validation period.

In conclusion, an empirically generated brief procedure code list based on ICD-9-CM describes almost all surgical procedures performed at a Ugandan referral hospital. Such a standardized procedure coding system may enable better surgical data collection for research and quality improvement in low-resource setting hospitals.
“Non-Functional” Adrenal Adenomas and Incident Cardiometabolic Outcomes

Diana Lopez
Harvard Medical School, Francis Weld Peabody Society, Class of 2016

Anand Vaidya, MD, MMSc
Division of Endocrinology, Diabetes and Hypertension, Department of Medicine,
Brigham and Women’s Hospital

Adrenal incidentalomas (AIs) are masses detected during radiological studies conducted for reasons other than the evaluation of the adrenal glands. The prevalence of AIs varies from <1% in young patients to 7-15% in the elderly. The majority of AIs are benign or nonfunctional adenomas (NFAs). However, recent evidence suggests that NFAs are associated with increased risk of cardiometabolic risk factors.

We conducted a longitudinal nested case-control evaluate the hypothesis that NFAs may increase the incidence of adverse cardiovascular and metabolic outcomes. Using an institutional database, we identified patients with an abdominal CT or MRI performed between 1991-2014, excluding those with any known adrenal hormonal disorder or malignancy. We then identified patients with an ICD-9 or physician diagnosis of any benign adrenal neoplasm (n=1346) and identified potential controls (matched 3:1 by age, gender, and race) as individuals with no adrenal neoplasm diagnosis (n=4041). Cases were confirmed after identification of an adrenal adenoma on imaging with no evidence of adrenal hormone dysfunction (n=592). Controls were confirmed after verification of no adrenal neoplasm on imaging and excluding any hormone dysfunction (n=1198). Individual medical records were reviewed for demographic, past medical history, medication use, lipid profile, and endocrine lab tests. Longitudinal data was collected in patients with ≥3 years of follow-up (413 cases, 726 controls).

At baseline, NFAs were independently associated with a higher prevalence of prediabetes (OR=2.49 [95% C.I. 1.51, 4.12]), T2D (OR=1.70 [1.27, 2.26]), and hyperlipidemia (OR=1.43 [1.13, 1.81]). Longitudinally (mean 7.9y, range 3-23y), NFAs were associated with a significantly higher adjusted relative-risk of developing incident prediabetes and T2D, when compared to controls (RR=2.52 [1.54, 4.14], RR=1.75 [1.07, 2.85]). Cortisol values following 1mg dexamethasone suppression test were significantly higher among NFAs with baseline DM when compared to NFAs without baseline DM (1.29 ± 0.08 vs 1.04 ± 0.04 mcg/dL; P<0.01); however, they did not predict risk for incident DM. There was no association between aldosterone-to-renin ratio, or size of the NFA, and either prevalence or incidence of outcomes.

These results suggest that NFAs are independently associated with an approximately 2-fold higher risk of developing prediabetes and T2D. Whether “non-functional” adrenal adenomas produce glucocorticoids, and/or mineralocorticoids, that evade our current clinical practice and contribute to cardiometabolic outcomes warrants further study. The strengths of the study include the novelty of the hypothesis and large sample size. Limitations include the observational nature of the study and lack of standardized times for outcome assessments.
Sequence-specific suppression of alleles causing dominantly inherited retinal degenerations using the RNA-guided nuclease Cas9

Clara Men  
Harvard Medical School, William Bosworth Castle Society, Class of 2016  
Eric Pierce, MD, PhD  
Department of Ophthalmology  
Massachusetts Eye and Ear Infirmary

Dominant mutations account for a substantial proportion of inherited retinal degenerations (IRDs) either through haploinsufficiency or gain-of-function (GOF) effects. This project proposes a potential strategy to treat diseases caused by dominant GOF mutations by specifically suppressing the function of the mutant allele at the genetic level using the CRISPR/Cas9 system. After taking into account the likelihood of allele pathogenicity, we identified six targets suitable for this form of genome editing therapy, including mutations in the  RHO, BEST1, IMPDH1, SRNP200, PRPH2, and PRPF8 genes. Cas9 single-guide RNAs (sgRNAs) for these targets were tested in COS-7 cells with pEGxxFP plasmids containing either the mutated allele target sequence or the wildtype sequence of the identified genes. The efficiency of Cas9 cleavage was quantified by FACS, and we identified guides with a two-fold increase in specificity for mutant alleles over wildtype alleles for BEST1, PRPF8, and PRPH2. The rate of allele-specific targeting by Cas9 was then assessed in patient-derived and control fibroblasts by next-generation sequencing (NGS). In patient fibroblasts, we saw up to 17.5% indel formation in the mutant alleles and up to 1.5% indel formation in the wild-type alleles, suggesting specific targeting of pathogenic mutations. The RNA-guided Cas9 nuclease is a potentially useful tool for targeted therapy in IRDs. This is a proof of concept that genome editing tools could be used to provide long-term suppression of GOF alleles to treat dominant genetic diseases.
Provider experiences with uterine balloon tamponade for uncontrolled postpartum hemorrhage in health facilities in Kenya

Abirami Natarjan
Harvard Medical School, Walter Branford Cannon Society, Class of 2016

Thomas Burke, MD
Division of Global Health and Human Rights
MGH

Objective: To understand provider perceptions and experiences following training in the use of a condomcatheter uterine balloon tamponade (UBT) as second-line treatment for uncontrolled postpartum hemorrhage (PPH) in health facilities in Kenya.

Methods: As part of a qualitative study, interviews of facility-based providers who had managed PPH following comprehensive PPH training were conducted between February and April 2014. Facilities were purposively sampled to represent a range of experience with UBT, facility size, and geography. Interviews continued until thematic saturation was achieved. Interview transcripts were analyzed for themes.

Results: Overall, 68 providers from 29 facilities were interviewed, of whom 31 reported experience with UBT placement (25 midwives, 2 clinical officers, 4 medical officers). Qualitative analysis revealed several major themes. Providers used UBT appropriately within the PPH algorithm, although the timing and clinical severity of patients varied. UBT was most commonly used when bleeding was unresponsive to uterotonic, hysterectomy was unavailable, and referral times long. Providers reported that bleeding was arrested following UBT use in all except one patient, who had a suspected coagulopathy. Most providers described UBT as technically easy to use, although three described initial balloon displacement.

Limitations: The present study had several limitations. Although a diverse sample of providers was purposefully included, practices at each of the facilities involved might not necessarily reflect those at other health facilities in Kenya. Furthermore, the interview-based findings were grounded solely on provider recollection, which could be potentially affected by either social desirability or recollection bias.

Conclusion: UBT has been readily accepted by providers at all levels of training and is being incorporated into the existing PPH management algorithm in Kenya.
Emergency hysterectomy for uncontrolled postpartum hemorrhage may be averted through uterine balloon tamponade in Kenya and Senegal

Anna Alaska Pendleton
Harvard Medical School, Walter B. Cannon Society, Class of 2016

Thomas F. Burke, MD
Division of Global Health and Human Rights
Massachusetts General Hospital

Postpartum hemorrhage (PPH) is responsible for greater than one third of maternal deaths in sub-Saharan Africa. The Massachusetts General Hospital Division of Global Health and Human Rights has previously designed and implemented a uterine balloon tamponade (UBT) package for uncontrolled PPH called Every Second Matters for Mothers and Babies – UBT™ (ESM-UBT). To date, ESM-UBT has been implemented in eight resource-limited countries, and multi-country preliminary analysis has demonstrated 98% survival of women with uncontrolled PPH if delivery occurred at an ESM-UBT facility. The purpose of this study was to investigate the impact of ESM-UBT on medical doctor decisions regarding emergency hysterectomy for uncontrolled PPH in Kenya and Senegal.

The subjects for this study were all medical doctors, identified from the authors’ Kenya and Senegal ESM-UBT database, who met the following criteria: (1) the provider had received ESM-UBT training, (2) the provider had implemented UBT in a case of uncontrolled PPH since training, and (3) the provider had the capability of performing emergency hysterectomy for PPH at the facility at which he or she inserted a UBT device. Interviews were conducted between January and February of 2015. Ethical approval was obtained from the Partners Healthcare Human Research Committee and the Maseno University Ethics Review Committee. Semi-structured interviews using a standardized guide were voice-recorded, transcribed, and independently analyzed and coded by two researchers using NVivo 10 software.

Thirty of the 31 (97%) medical doctors who fulfilled the inclusion criteria in the two-country database were interviewed. Twenty-eight of the 30 (93%) interviewed providers reported having witnessed at least one PPH-related maternal death in their careers. Collectively the interviewed medical doctors had placed over 80 UBT devices for uncontrolled PPH since ESM-UBT training.

All 30 providers responded that UBT controlled hemorrhage and prevented women from being taken to emergency hysterectomy. Twenty-six of the 30 (87%) responded that if they had not received ESM-UBT training they would have performed emergency hysterectomies in the cases of uncontrolled PPH that they instead successfully managed with UBT devices. All 30 providers reported that they would continue to use UBT devices in future cases of uncontrolled PPH.

These preliminary data suggest that following ESM-UBT training, emergency hysterectomy for uncontrolled PPH may be averted by use of uterine balloon tamponade. Further research is needed to quantify the impact of ESM-UBT on rates of emergency hysterectomy, to understand the optimal use of ESM-UBT, and to devise successful expansion and sustainability strategies.
Optimization of cost while improving quality of care is a central focus of national health reform. One major predictor of high cost of treatment is mental health comorbidity—on average, patients with a mental health diagnosis are 2.2 times more expensive than patients without a mental health diagnosis. In addition to mental health diagnoses, there are other behavioral health issues that may not result in a diagnosis, but still predict increased rates of health care utilization. This increase in utilization is theorized to be due to a decreased ability to care for self and high rates of unnecessary care, which may further present risk for unintended negative effects. Therefore, given the potential for significant improvement of health status and reduction in health costs, patients who may benefit from behavioral health referral are an important cohort for identification.

Structured administrative data, lab results, and free text notes were collected from the Partners Research Patient Data Registry (RPDR) for all patients with at least one visit to a primary care provider at Brigham and Women’s hospital. Of this cohort, patients with at least one visit to behavioral health were selected. Finally, patients were excluded if they did not have at least one clinical encounter both greater than 120 days before and greater than 120 days after their first behavioral health visit, leaving a cohort of 12,759 patients. Of these patients, 6057 had increased healthcare utilization following their first behavioral health visit, while 6702 had decreased healthcare utilization.

RPDR data was used to construct an initial feature matrix of approximately 17 million features. The feature matrix then entered a three-fold cross-validation, which split the data into three randomized pairs of training data and testing data. The resulting random forest classifiers were able to predict the following: decreased healthcare utilization (AUROC 0.74), healthcare utilization above the 95th percentile (AUROC 0.86), and healthcare utilization above the 99th percentile (AUROC 0.88).

The predictive models created for this research are both an improvement over comparison prior probabilities and compare favorably to similar studies. These methods may be used to improve the timeliness and accuracy of referrals to behavioral health services, improving patient physical and mental health and reducing the financial costs associated with behavioral health comorbidity.
National Trends in Incidence of Acoustic Neuromas Based on the Nationwide Inpatient Sample Database

Jinesh Shah
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2016

Samuel J. Lin, MD, MBA
Division of Plastic Surgery, Department of Surgery
Beth Israel Deaconess Medical Center

Acoustic neuromas (AN) are slow growing benign tumors of the eight cranial nerve (vestibulocochlear nerve). Their incidence in literature has been reported anywhere from 0% to 2.7% based on different short term and long term studies. While these tumors constitute 80% to 90% of cerebellopontine angle tumors, their true incidence and trends in diagnosis and treatment are unknown, especially over long periods of time. This study was the largest database analysis to evaluate incidence and trends in AN diagnosis and treatment in the US using the Nationwide Inpatient Sample (NIS). This information is critical for determining effects of improving methods of diagnosis and treatment of AN, in addition to establishing a baseline for future studies evaluating effects of changing infrastructure, demographics, and policies.

We analyzed 25 consecutive years of data from the NIS database (1988 – 2012), forming the largest and longest such database for AN, consisting of 137,818 patients. This database has not previously been used to report on AN. We split the data into four geographical regions and evaluated trends over time, including subgroup analysis by Age, Hospital Size, Income Quartile, Expected Primary Insurance Payer, Patient Race, and Local Population.

Total number of AN cases in the United States has increased from 3569 in 1988 to 5900 in 2012 (p=0.156). The only region with significant increase is the South, from 1101 to 1906 cases (p= 0.007). In subgroup analyses, age was most directly correlated to incidence, with highest incidence and growth rates in the 65+ group. White race, and lowest income quartile were subgroups with the highest incidence, and most of these cases presented at large hospitals (p < 0.05).

While there has been a general increase in incidence of AN over the past 25 years, it is unclear whether this is due to improved detection or more aggressive intervention. A likely cause is the aging American population, as demonstrated by highest incidence and growth among those aged 65 and higher. Self-reported white race reported the highest incidence, consistent with national demographics. Since large hospitals are best equipped to diagnose and intervene on AN, it is not surprising that a majority of cases originated at these centers. Lastly, a possible explanation for the disproportionate proportion of AN patients belonging to the lowest socioeconomic quartile is related to healthcare resource utilization in emergency situations and consequent incidental discovery and unlike related to income related environmental exposures.
Effect of Obstructive Sleep Apnea Risk on Postoperative Respiratory Complications

Christina H. Shin
Harvard Medical School, William Bosworth Castle Society, Class of 2016

Matthias Eikermann, MD
Department of Anesthesia, Critical Care, and Pain Medicine
Massachusetts General Hospital

Background: Postoperative respiratory complications (PRC) are associated with significant morbidity, mortality, and hospital costs. Obstructive sleep apnea (OSA), which is often undiagnosed in the surgical population, may be a contributing factor. Therefore, we have created a new prediction score in order to better capture the impact of OSA risk on postoperative outcome.

Objective: To develop a Score to predict Preoperative Obstructive Sleep Apnea (SPOSA) based on data available in electronic medical records and to investigate the effect of OSA risk on incidence of PRCs.

Methods: This is an observational study of 99,353 surgical patients at Massachusetts General Hospital between January 2007 and August 2014. OSA was defined as the occurrence of an OSA diagnostic code preceded by a polysomnography procedure conducted at Partners HealthCare. A set of variables that could potentially predict OSA was selected a priori and a multivariable logistic regression analysis with automatic forward selection was used to develop our score. Reclassification analysis was conducted to evaluate if the addition of post-extubation deoxygenation adds clinically important information to the prediction of OSA. Multivariable logistic regression analyses were performed to analyze the effect of OSA risk, as defined by SPOSA score, on the incidence of PRCs within 3 days of surgery, a composite outcome including pneumonia, pulmonary edema, reintubation and respiratory failure.

Results: A total of 2,079 patients met criteria of OSA. Predictors for OSA included BMI>25, ASA score of 2 or greater, and various comorbidities. The score yielded an area under the receive-operating characteristic curve of 0.82, an improvement from currently used screening scores. Inclusion of early post-extubation desaturation did not change this finding. An optimal cut-point of SPOSA > 34 was identified as high OSA risk using the Youden Index. As validation of the SPOSA score, our prediction model predicted noninvasive ventilation among patients with high OSA risk (odds ratio 1.38, 95% confidence interval 1.20-1.59). PRCs occurred in 6.9% of those identified as high risk for OSA and 3.4% of those identified as low risk for OSA. OSA risk was significantly associated with incidence of PRC (odds ratio 1.21, 95% confidence interval 1.10-1.33).

Conclusions: The SPOSA provides very good prediction of OSA by using electronic medical records, and predicts the occurrence of respiratory complications. Its use will allow providers to classify patients in risk groups of OSA prior to hospital admission and may help to reduce perioperative consequences of OSA.
Committed to Leadership: A Landscape Analysis of Leadership Training in the Medical School Curriculum

Diana Wohler  
Harvard Medical School, Francis Weld Peabody Society, Class of 2016

Erin Sullivan, PhD and Somava Stout, MD MS  
Harvard Medical School  
Center for Primary Care

Little is known about the availability of or desire for leadership training in the medical school curriculum, particularly for students who are interested in primary care fields.

A landscape analysis of leadership training in the medical school curriculum was conducted via an online survey of medical students and a database search of medical school curricula and courses. To determine the current offerings in leadership training in U.S. medical school curricula, a search of the AAMC Curriculum Inventory was performed using the keywords “teamwork” and “leadership”.

To determine which leadership competencies to study in our survey, we compared the competencies assessed by the validated NHS Clinical Leadership Competency Framework Self-Assessment and subtracted those required of U.S. allopathic medical schools by the LCME. This resulted in five leadership competencies assessing teamwork, team leadership, and change leadership. An online Qualtrics survey was constructed using these five competencies as a framework to assess the sufficiency of curricular opportunities for leadership training, the desire to pursue these curricular opportunities, self-perception of leadership competencies and behaviors, and career interest in leadership and primary care. This survey was distributed nationwide to U.S. medical students via the snowball technique and via the email listserves and social media networks of national medical student organizations. An incentive to enter a lottery for one of four $100 Amazon gift cards was offered to students who completed the survey in order to mitigate selection bias.

The quantitative survey results were analyzed with Qualtrics software to determine mean and standard deviation of responses, and sub-groups were analyzed with manually applied filters, cross-tabulations and chi-square analyses. The database search data was analyzed qualitatively for key aspects of teamwork and change leadership, according to predetermined definitions and competencies.

Our survey results demonstrated that respondents are interested in learning about teamwork, managing teams, identifying the context for change, facilitating transformation, and encouraging improvement and innovation. With regards to leadership behaviors, survey respondents identified “volunteering to lead the team” and “identifying the drivers of change” as areas of relative weakness.

The database search demonstrated that many U.S. medical schools provide curricular opportunities for working within teams, but a minority provided opportunities to learn team management or change leadership.

Leadership training for medical students, including those interested in primary care, is desired but still lacking in U.S. medical school curricula.
Trends in Direct-to-Consumer Advertising of Prescription Contraceptives
Min Wu
Harvard Medical School, Oliver Wendell Holmes Society, Class of 2016

John D. Seeger, PharmD,DrPH, Jerome Avorn, MD
Division of Pharmacoepidemiology and Pharmacoeconomics
Brigham and Women's Hospital

Objective: Despite much speculation about the role of direct-to-consumer advertising (DTCA) in increasing demand for prescription contraceptives in the United States, there is little published research on this topic. We sought to quantify the prevalence and magnitude of DTCA for prescription contraceptives over the last decade.

Study Design: Using cross-sectional data from January 2005 through December 2014, we performed descriptive analyses on trends in DTCA expenditure for prescription contraceptives. We also quantified the amount of DTCA according to contraceptive method category and individual brand.

Results: During the study period, pharmaceutical companies spent a total of $1.57 billion in the United States on DTCA of prescription contraceptives. Annual expenditure for contraceptive DTCA reached a peak value of $260 million in 2008, with a progressive decline to a nadir of $69 million by 2013. Of the contraceptive methods, oral contraceptive pills (OCPs) have been the most heavily promoted, with Yaz (drospirenone/ethinyl estradiol) – the most advertised brand – accounting for $347 million of cumulative DTCA expenditure. However, DTCA spending on OCPs peaked in 2007 and was overtaken in 2012 by the DTCA of long-acting reversible contraceptives (LARCs), the contraceptive method now receiving the largest amount of DTCA promotion.

Conclusions: Direct-to-consumer advertising is a major form of promotion for prescription contraceptives. Recent trends in DTCA expenditure indicate a shift from promotion of the OCPs to the LARCs. Direct-to-consumer advertising’s effect on provider and patient utilization of various contraceptive methods has yet to be determined.