73rd Annual
Soma Weiss
Medical and Dental
Student Research Day
January 17, 2013

Book of Abstracts

HARVARD MEDICAL SCHOOL
Scholars in Medicine Office
The Soma Weiss Student Research Day

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

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

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

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

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

73RD ANNUAL
Soma Weiss Student Research Day
January 17, 2013

Poster Sessions
1:00 - 4:00 PM
Atrium of the Tosteson Medical Education Center
260 Longwood Avenue, Boston, Massachusetts

Reception
3:00 – 4:00 PM
Atrium of the Tosteson Medical Education Center

Student Presentations and Poster Awards
4:00 – 5:00 PM
Room 250, Tosteson Medical Education Center

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

Introductions  Patricia D’Amore, PhD, Professor of Ophthalmology (Pathology), Schepens Eye Research Institute
Chair, Faculty Committee for Student Research

Student Speakers  Vinayak Muralidhar (London)
Influence of Metabolic Regulation on Primary Cell Proliferation and Differentiation
Alexander Ryu (Peabody)
Are Lower Rates of Spending Growth Here to Stay? Analyzing the National Spending Slowdown 2007-2010
Hoi See Tsao (Castle)
Changing the Way We Approach Medically Complex Children: A Screen for Unmet Needs
Jia Zhu (Cannon)
Rare Variants in Genes Implicated in GnRH Deficiency in Constitutional Delay of Puberty Patients

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 Community Health Delivery or Service
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Improving Obstetric Referrals in Developing Countries: Early Experiences from Process Improvement Efforts in Assin-North, Ghana

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Women in developing countries often face serious health risks during pregnancy and delivery due to poor access to early and appropriate referrals. Despite studies that show clear linkages between timely referrals and improved maternal outcomes, challenges still remain in the referral process, particularly in rural communities. Few studies have functionally mapped out these challenges or examined how process improvement methods can be used to address them. Using the example of a referral network in a rural district in Ghana, we investigated baseline referral systems in obstetrics, with a focus on systemic bottlenecks and strategies to improve the process.

Our study used a mixed methods approach. For the quantitative component we reviewed hospital registers for major causes of referral in obstetrics, and delay indicators such as time from arrival at hospital to definitive treatment. The qualitative component consisted of semi-structured interviews of 18 health professionals at different levels of care within the Assin-North Municipal Assembly of Ghana. We assessed existing referral protocols, perceived barriers, and process improvement methods to streamline referrals.

Preliminary quantitative findings show that between January - June 2012, the leading causes for obstetric referrals from feeder facilities to the district hospital were prolonged labor, retained placenta, postpartum hemorrhage, malpresentation of baby, and premature rupture of membranes. From the district hospital to tertiary care hospitals, the leading cause of referrals was severe eclampsia. Delay indicators were not obtained due to poor documentation. Findings from our qualitative study demonstrate that the referral system was not standardized, with important gaps noted in processes related to recognizing danger signs, alerting receiving units, accompanying critical patients, documenting referral cases, and giving and obtaining feedback. Providers further explained that these gaps were often due to transportation and communication barriers, poverty, negative attitudes by hospital staff towards referred clients and accompanying nurses, clients’ fear of dying at the hospital, and clients’ delay in seeking earlier care. To address these barriers, providers suggested standardizing referral protocols, providing continuous staff training, improving transportation systems, ensuring reliable data management systems, and strengthening community engagement.

Addressing faulty referral processes hold tremendous promise for reducing maternal mortality, especially if they target challenges at both facility and community levels. To further inform the implementation of effective interventions to improve referrals, improved monitoring and evaluation practices are necessary to identify effective practices and ongoing or new gaps to better understand ways to strengthen referral processes for pregnant women, particularly in developing countries.
An Expression Analysis of Galectin-1 Ligands in Melanoma Progression

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Cell surface carbohydrates and proteins (lectins) that bind them are conspicuously elevated in cancer. These sugar structures and lectins are critically involved in cancer cell motility, invasion and/or migration that ultimately evoke the lethality of cancer. There is a convincing body of evidence suggesting that β-galactoside-binding lectin, Galectin-1 (Gal-1), is a major glycopathogenic mediator of melanoma progression and metastasis. Studies show that melanoma-derived Gal-1 has a major impact on T cell-mediated anti-melanoma immunity. While most labs have focused on Gal-1 and its functional activity in these malignancy-related events, few have studied the functional expression of Gal-1 carbohydrate-binding determinants found on the surface of melanoma cells. In our lab, we have exciting preliminary data showing that human melanoma cells express a robust level of Gal-1-binding carbohydrates, including the membrane protein(s) that display them, that are conspicuously absent on normal melanocytic cultures. Differential expression of these Gal-1-binding carbohydrates on distinct glycoproteins, operationally referred to as Gal-1 ligands, could, therefore, functionally correlate with malignant progression of human melanoma. Here, we performed double immunohistochemical analysis on a cohort of human skin sections containing both benign and malignant melanocytes using a new Gal-1–human Ig chimeric probe, which recognizes native Gal-1 ligand, and a moAb against melanocyte antigen S100. Sections were then counterstained with DAPI. We found that Gal-1 ligands were generally expressed at a high level and evenly distributed over the entire melanoma lesion (Gal-1 ligand/S100+ cells), whereas Gal-1 ligands were not expressed on adjacent benign epidermal melanocytes (Gal-1 ligand/S100− cells). Using TissueGnostics software, we quantified the level of Gal-1 ligand and/or S100 on individual DAPI+ cells in skin sections and found the Gal-1 ligand was significantly higher on S100− malignant melanocytic cells than on non-malignant melanocytes. Future studies will include a larger cohort of skin specimens at different stages of transition to malignancy to determine whether a gradient of Gal-1 ligand expression in benign, pre-malignant and malignant tissue can be a useful predictor of malignant potential. These findings provide novel molecular insight into the glyco-histopathology of melanomas and a putative glycomic biomarker of malignancy and clinical outcome.
The DNA Damage Response in Naïve and Primed Human Pluripotent Stem Cells

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Pluripotent stem cells have elicited much attention for their therapeutic potential. Given that such stem cells can give rise to all cells of the body, these cells are fundamentally important for regenerative medicine. Much of the data concerning pluripotency has been derived from mouse and human embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). In 2007, a paradigm shift in conventional pluripotency occurred upon the discovery of two unique states of pluripotency in mESCs. Canonical mESCs were called naïve, while a newly discovered metastable pluripotent state was termed primed because cells in this state were ready for lineage specification. Primed mouse ESCs resembled human ESCs whereas naïve mouse ESCs were dramatically different. Recently, advances in reprogramming have also generated putative naïve human iPSCs, which appear to have many of the properties of mESCs such as amenability to genetic manipulation and clonal isolation. These benefits may thus allow naïve human iPSCs to become the new standard for pluripotent research, with applications beyond hESCs and primed iPSCs.

Naïve human iPSCs have opened of a new chapter of pluripotency which hopes to bridge the divide between rodent and human pluripotency. However, to date, there has been virtually no functional analysis or characterization of the naïve human pluripotent state. We hope to better understand this newly discovered pluripotent state by analyzing the regulation of the tumor suppressor p53. Our lab and others have shown that p53 is intriguing for many reasons. p53 is known to be involved in inhibiting the pluripotent state but is critical for maintaining genomic stability. Most interestingly however, is that iPSCs and ESCs are hypersensitive to DNA damaging agents and p53 activation. We have taken advantage of naïve and primed iPSCs and ESCs in order to understand pluripotency and p53.

To conduct this analysis, we derived naïve human iPSCs from primary human fibroblasts and compared them to primed pluripotent cells upon induction of genotoxic stress. We observed activation of DNA damage sensors, p53 accumulation and activation of mediators of apoptosis. Naïve pluripotent cells appear to be more sensitive to genotoxic stress compared to primed pluripotent cells. Naïve cells accumulate p53 rapidly and robustly, especially when compared to genetically matched primed cells. It is unclear, however, whether the activation of downstream apoptotic pathways is directly correlated to these levels of p53.
LeFort III advancement improves the position of the midface in patients with syndromic craniosynostosis. The purpose of this study is to understand the changes that occur in the position of the mandible after midfacial advancement using distraction osteogenesis (DO). Information about how the mandible moves with midfacial advancement will help clinicians counsel patients regarding changes in facial profile and the need for future operations.

Data were collected from patients with syndromic craniosynostosis who had midfacial DO performed at a tertiary care center. Linear and angular measurements were traced on pre- and post-operative cephalograms. Preoperative measurements were compared to standard age and sex matched data from the Michigan Growth Study (Riolo et al., 1974) and to postoperative measurements. Mandibular measurements included ramus height (Co-Go), body length (Go-Me), mandibular length (Co-Pg), and gonial angle (Ar-Go-Me). Horizontal and vertical facial changes were compared using maxillary and mandibular protrusion/retrusion angles (SNA, SNB), and mandibular plane angle (SN-GoMe). A paired t-test analyzed significant differences between preoperative and growth study variables as well as between pre- and post-operative variables. Each cephalogram was traced twice to establish intra-examiner reliability.

Twenty-seven patients (15 males and 12 females) with syndromic craniosynostosis underwent LeFort III midfacial advancement with DO at a mean age of 11 years and 2 months. Comparison of preoperative mandibular measurements to standard growth study data showed that patients with syndromic craniosynostosis have a shorter mandibular body (mean difference for Go-Me, 22.46 mm ± 6.88), shorter mandibular length (Co-Pg, 20.50 mm ± 8.01), and a larger angle formed by the ramus and mandibular body (Ar-Go-Me, 6.66 mm ± 7.30). Only 18 of the 27 patients had a pre- and post-operative cephalograms taken within a 2 year period. In these 18 patients, the maxilla moved forward (SNA, 70.56° ± 7.58 to 84.26° ± 7.34), the mandible moved backward (SNB, 83.23° ± 8.85 to 79.21° ± 7.35), and the mandible moved downward (SN-GoMe, 34.13° ± 10.75 to 39.12° ± 10.70). There were no significant differences for intra-examiner reliability.

As compared to the standard norms, patients with syndromic craniosynostosis have a shorter mandibular body, smaller mandibular length, and greater gonial angle. Correction of midfacial hypoplasia using LeFort III advancement with DO results in an inferior and posterior movement of the mandible. Clinicians can use this information to counsel their patients regarding changes in facial profile and the need for adjunct procedures.
Comparative Gene Expression Analysis of Calcific Aortic Stenosis in Bicuspid and Tricuspid Aortic Valves

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Bicuspid aortic valve (BAV) is a congenital heart malformation resulting from abnormal fusion of aortic valve leaflets—most commonly the right- and non-coronary leaflets (R-NC) or the right- and left- coronary leaflets (R-L). BAV is highly associated with valvular calcification, and many patients with BAV develop aortic stenosis. Though BAV and associated aortic valve disease accounts for significant morbidity and mortality in the United States, current understanding of the pathological link between the two is limited.

In this study, we utilized RNA sequencing and enrichment analysis to elucidate molecular pathways of aortic stenosis in patients with either tricuspid aortic valve (TAV) or BAV. In doing so, we sought to understand how mechanisms of pathogenesis differ between patients with TAV and BAV.

Aortic tissue samples collected from two groups—patients with stenotic bicuspid aortic valves (n=10) and patients with stenotic tricuspid aortic valves (n=9)—were compared to a control group of patients with non-stenotic tricuspid aortic valves (n=10). RNA sequencing was performed on each tissue sample to generate normalized expression values for ~31,000 genes. Molecular pathways enriched in each of the two groups, relative to the controls, were identified using GeneGo MetaCore software.

Cell cycle pathways, notably the regulation of G1/S transition, were enriched in both non-stenotic TAV and BAV tissue, suggesting an increase in proliferative activity relative to the control group. Developmental pathways involving NOTCH1 signaling were more significantly enriched in the stenotic BAV tissue than stenotic TAV tissue. This is an interesting finding as NOTCH1 has been implicated in valve calcification.

Preliminary analysis has suggested the existence of both similar and unique pathways enriched in tissue from stenotic BAV and TAV.
Tibial Eminence Fractures: Suture vs. Screw fixation – Does anterior fragment elevation matter?

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Tibial eminence fractures occur most often in children and teenagers between the ages of 8 and 14, particularly in the setting of bicycle and sport-related accidents. Displaced tibial eminence fractures are managed surgically with reduction and fixation of the displaced fragment. Surgery can be done arthroscopically or through an open approach. Many different types of fixation techniques have been described. At our institution the two most popular techniques employed are suture fixation and screw fixation. Each type of fixation has its own set of advantages and disadvantages. There is a lack of literature comparing clinical and radiographic outcomes of these two fixation methods in children and teenagers. A dedicated study of fracture fixation outcomes in pediatric patients is still missing from the literature.

We set out to determine if suture fixation is superior to screw fixation with regard to elevation of the anterior portion of the tibial eminence fragment and subsequent functional outcome as assessed by pediatric - IKDC scores and reoperation rate. Children’s Hospital Boston electronic medical record database, PowerChart, was queried from January 2000 until January 2011. Patients that had surgery at Children’s Hospital Boston while being 18 years old or under were identified (n=123). Patients were excluded from the database due to lack of information on clinical notes (no follow-up available, n=23). Of the remaining pool, patients who underwent suture fixation (n=30) versus patients who received screw fixation (n=60) were investigated. We have collected biometric data and reviewed clinical notes of these patients. Clinical results involving complications such as arthrofibrosis, reoperations and ability to return to sports have been logged.

Further data to be revised includes elevations of the anterior portion of the tibial eminence fragment will be measured on postoperative radiographs. Subjects will be contacted to complete a pediatric IKDC form (or adult IKDC if age>18) and Marx activity scale form to determine if there are any differences between suture fixation and screw fixation for tibial eminence fractures with regard to current activity.

In this study we were limited by the diverse spectrum of information on the clinical notes. Some patients have detailed notes while others are lacking crucial points of information. However, we expect to be capable of successfully comparing these two arthroscopic techniques in order to find the most effective therapy in pediatric patients.
Base shade determination and the effect of ceramic modifiers in achieving superior color match

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Determining and matching tooth color is one of the most difficult challenges in clinical dentistry due to the subjectivity of perceptual evaluation, the polychromatic nature of teeth, and the limitations of dental shade. In recent years, computerized color matching (CCM) systems have been developed to enhance the precision of color matching. The usage of CCM systems allows for a non-biased, objective determination of tooth color and allows a better color matching system.

The purpose of this project is to determine the effect of ceramic modifiers in achieving superior color match through the use of a CCM system. Specifically, the focus of this project is to conduct a spectrophotometric assessment of the color shift by the use of modifiers. It is hypothesized that the appropriate usage of ceramic modifiers with correct concentrations on specific ceramic shades and thickness can provide predictable superior color reproduction.

The method of testing this hypothesis was creating sample ceramic discs and measuring specific parameters using a spectrophotometric analysis. The sample structures made in the lab consisted of ceramic disk, zirconia plate, and 5 mm thickness composite (mimicking a prepared tooth). To each set of samples a certain concentration of modifiers was added. Each sample was then baked, coarse polished, fine polished and measured to ensure that the thickness was between 0.9 mm and 1.1 mm. The method of measuring how the color shift was affected was done by a spectrophotometer. The parameters that were analyzed are: the color of the modifier, the concentration of the modifier, base shade, and thickness of ceramic disk.

The data that was created was that of the CIELAB color coordinated. The base shades used were NW0B and B1B. The ceramic modifiers used were pink, light orange, and a mixture of pink and light orange. The concentrations of these modifiers were 0.5%, 1%, 1.5%, 2%, 4%, and 6%. All of the samples have been created and analyzed using the CIELAB software. Graphs and tables have been made, and the final analysis of the data is currently underway.

The ultimate goal of this project is to determine a set of data values to be able to reference in dental practices. This seems to be a limitation thus far, as the replicability of the colors in clinical practice is still under assessment. The project has been very successful thus far and is nearing completion.
Mapping allelic variation in regulation of neuropsychiatric disease: \textit{CACNB2}

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Many recent genome wide association studies (GWAS) have reproducibly identified genomic loci with strong statistical associations to neuropsychiatric disease. A number of these associations map to subunits of the voltage-gated L-type calcium channel. In one recent cross-disorder study, significant association to disease was detected within an intron of one channel subunit (\textit{CACNB2}). \textit{CACNB2} encodes a \(\beta\)-regulatory subunit that likely controls much of the physiologic variation in channel function. Review of data emerging from the ENCODE Consortium suggests that the \textit{CACNB2} index SNP falls within a region of DNase hypersensitivity and within a likely binding site for transcription factors, suggesting that this SNP may be involved in regulation of transcription. A risk-associated genotype in this non-coding region may be associated with disease by cis-acting regulation of the expression level of a component of the calcium channel. We hypothesized that expression level of \textit{CACNB2} is functionally correlated with genotype and that change in expression of the \(\beta\) transcript leads to a change in cellular physiology that predisposes to pathology of schizophrenia, bipolar disorder, and other neuropsychiatric disorders.

Our experimental approach takes advantage of the heterozygosity that exists within each individual’s genome to make internally controlled measurements of allelic expression. We have implemented an innovative technology to quantify allele-specific expression using taqman-based oil emulsion droplet digital PCR. This technique allows us to interrogate abundance of alleles within an individual using microfluidic digital counts of RNA molecules. Using bioinformatics techniques, we can leverage the observed pattern of allelic imbalance to impute the most likely functional SNP using known genomic information.

Using this approach, we have measured allele-specific expression within \textit{post mortem} samples from 105 individuals obtained from the Stanley Medical Research Institute repository. Preliminary results suggest that there are cis-acting genetic regulators of expression at the locus. Further effort on the project is aimed at understanding the contribution to allele-specific expression driven by each alternative isoform of \textit{CACNB2}. Subsequent goals include mapping the functional regulatory influence responsible for observed allelic differences in expression within the genome and within the human brain.

Our project aims to elucidate one cellular pathway involved in neuropsychiatric disease etiology. Our results may add to the current understanding of the L-type calcium channel and cellular calcium homeostasis. Furthermore, this study may serve as a model by which the functional implications of other GWAS results may be interrogated in the future.
Predicting the Incidence of 30-day Surgical Complications with Health Related Quality of Life

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Effective management of the postoperative process by the surgical institution and the patient is necessary to mitigate preventable complications. We hypothesize that patients with a high burden of disease are unable to effectively manage the postoperative self-care process. A Health Related Quality of Life (HRQL) survey can be used as a proxy for burden of disease, measuring the combined social, physical, and emotional impairment experienced by our patients. If an association is established through this study, HRQL assessment tools may be used in the future to identify surgical patients who would benefit from special measures (i.e. additional follow-up, education, specific diet and exercise plans, or social services) to prevent surgical complications and increase their general health immediately following surgery.

We began a prospective study to explore the association between preoperative HRQL and postoperative complications within 30 days of surgery. The population of interest includes adult patients scheduled for non-traumatic general and vascular surgical procedures, including colectomy, proctectomy, pancreatectomy, abdominal aortic aneurysm repair, aortoiliac stenting, and lower extremity bypass. HRQL is measured before surgery using the Patient Reported Outcomes Measurement Information System combined survey (PROMIS-29). Subject data from the National Surgical Quality Improvement Program (NSQIP) database will be matched to the HRQL survey responses. The relative risk of 30-day postoperative complications will be calculated between the following groups of PROMIS-29 T-score values: ±1 standard deviation (SD), <−1 SD, and >1SD. Multivariate analysis will resolve whether the association between the HRQL data and the primary outcome is modified or confounded by various clinical and demographic factors.

At least 30 cases with complications are required to perform the statistical tests outlined above. At an estimated 33% complication rate across the surgeries of interest, we will need to recruit at least 100 patients to achieve this. Currently, 27 patients have completed the HRQL assessment tool. Unfortunately, ad hoc data analysis cannot be performed because the primary outcome data on postoperative complications is available from the NSQIP database 3-months after surgery. Patient recruitment will continue until sufficient case volume is achieved.
A Team-Based Model for the Integrated Management of Chronic Pain in Primary Care

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The use of prescription opioids has risen significantly in the U.S. in the last two decades, contributing to a dramatic rise in opioid-related deaths. Many of these prescriptions are written by primary care providers (PCPs), who may have limited skills to assess the risk of abuse and limited resources to monitor therapy. Current systems of care for patients on chronic opioid therapy cause significant dissatisfaction among both patients and providers and may lead to high resource utilization. In response to these issues, this intervention adapted chronic disease management tools that have been used successfully for other conditions (e.g. diabetes, CHF) to improve the quality of care for patients on chronic opioid therapy. Key components of these models are a team approach, standardized management protocols and the use of shared medical appointments to provide group education and support.

The goals of this program are to improve coordination of care, to incorporate the expertise of a clinical pharmacist, to build support through groups, to improve self-management skills, to increase provider confidence in assessing pain and addictions risk, and to decrease opioid diversion and abuse. After an initial assessment visit with a physician and clinical pharmacist focused on pain and medication history, patients participate in six shared medical appointments with 6-10 other patients. Visits incorporate check-in and a planned curriculum including such subjects as exercise, pacing and mental health. After the groups, patients have short individual visits to review and refill medications. After patients complete the program, the PCPs are offered management guidance and continued monitoring from the clinical pharmacist.

Data is being collected on patients’ pain and function, depression, and appropriate use of medications; and provider satisfaction and opioid prescribing confidence before and after the intervention. To examine healthcare utilization, charts are reviewed for total and unscheduled visits pre- and post-intervention. The data is currently being analyzed. Early results trend towards improved functional status and depression rates. Patients report satisfaction with group visits as a learning tool and a connection to others with similar problems.

Based on early data and patient comments, chronic disease management tools such as pharmacy visits, shared medical appointments, and standardized protocols may help to improve the quality of chronic pain management in the primary care site and improve provider satisfaction. Results from this pilot may help to show whether they improve patient satisfaction, reduce utilization, and improve the detection of opioid abuse.
Three-dimensional in vivo blood flow mapping in tumors using optical frequency domain imaging

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Angiogenesis in the tumor microenvironment is a chaotic process that results in a dysfunctional vascular network. Unlike normal blood vessels, tumor vessels are dense, tortuous, and leaky. The disorganized nature of the tumor vascular network often leads to unequal perfusion to different parts of the tumor. While some vessels see high blood flow rates, others are virtually stagnant. Knowing how blood flow changes as a tumor develops its vasculature is a critical step in our understanding of tumor angiogenesis. In addition, our ability to more fully understand how anti-angiogenic and chemotherapeutic treatments affect tumor vessels relies on our ability to monitor blood flow.

Unfortunately, existing methods for measuring blood flow are limited by low resolution, long imaging times, or single vessel measurements. Here, we use optical frequency domain imaging (OFDI) to measure blood flow in individual vessels over an entire tumor volume. Our technique uses the light scatter of moving objects, which changes over time as a function of velocity. Using these measurements we are able to generate a three-dimensional map of blood flow within a tumor. Our results demonstrate the potential for OFDI to offer a unique tool for studying blood flow in vivo.
CommCare: Advancing Pediatric Health with a Phone-based Tool for Community Health Workers in a Resource-poor Setting

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CHWs are becoming a quintessential model for effective primary care. In Kenya and other low-resource settings, however, CHWs are often trained but not given continuity in mentorship or supervision, lacking in adequate tools for health care delivery, and must bear their work in isolation. To overcome the challenges faced by CHWs, a cost-effective method of providing them with the skills, continued mentorship, supervision, and tools for delivery would be given with CommCare, an open-source mobile phone software.

Training the CHWs and collecting data on their proficiency with the mobile phones and software would make piloting of the prototype software by the CHWs in the field possible. This piloting process would allow for subsequent development of the CommCare application to suit the needs of this community's needs in Kenya.

In collaboration with the Harvard organization, Common Hope for Health (CHH), the Government of Kenya, and the indigenous St. Paul's Health Center, run jointly with the Ugunja Community Resource Center, I trained CHWs to use the preliminary CommCare application made for a similar project in India and tested their proficiencies throughout the training process. I recorded results throughout both the training and the pilots that followed, and reported back to our software development partners, Dimagi.

During the training process, various glitches in the coding were discovered and reported back to the software developers for coding clarification. Errors included problems with entering household information, permissions, how to call emergency numbers when necessary, and simple formatting issues pertinent to the specific cell phone model on which the application would be installed. CHWs often faced ancillary challenges in the field, including requests for medications, mosquito nets, and additional information not provided by the auditory and visual aids of the CommCare application. It was clear that the community wanted more information than what the prototype was offering at the time of the pilot.

Overall, the CHWs were excited to use the new program, but it became evident that many hours would have to be invested for proper training based on each CHW's past exposure to technology. Other unexpected factors, such as visual acuity, came into play as well and will be included in the screening process for future trainings.

Limitations of this project in the future include CHWs falling ill, cell phones lost, broken or stolen, inaccurate data entry, and the sheer manpower required for training of the 40 CHWs planned for the final project implementation.
Employment after Stroke in Trivandrum, India

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Objective: To determine what proportion of previously employed stroke patients in India who report mild disability (modified Rankin scale ≤ 3) return to work (RTW) 3 months to 2 years after the acute event and examine the association between psychosocial and social support factors among mildly disabled stroke patients with a successful RTW.

Background: Stroke is a growing problem in India and costs billions of dollars in direct care costs, lost productivity, and long term support. A successful RTW after stroke has been shown to not only improve economic circumstance, but also quality of life, and overall life satisfaction. The percentages of stroke patients who return to work vary widely across the globe and in India specifically, there is no current published data on these patients.

Design: Five eligibility characteristics were used to select study participants: age between 18 and 60 years old, modified Rankin score ≤ 3, employed prior to stroke, first ever stroke, stroke occurred between 3 months to 2 years prior to date, and no other diseases/conditions that may interfere with disability. Using patient interviews and chart review we collected details about the acute stroke event and information about socio-demographic variables, including employment prior to and after stroke, as well as potential reasons for unemployment. Previously validated instruments were used to assess anxiety and depression (Hospital Anxiety and Depression Scale) and social support (Duke-UNC Functional Social Support Questionnaire [FSSQ]). Descriptive analysis was used to determine those RTW and chi-square tests will be used to assess the association between selected respondents’ characteristics (presence of depression, psychological barriers, and social support factors) and their responses.

Results: We collected information on 30 out of an expected 150 patients. Preliminary results show that overall, 62% of patients RTW after stroke. Those that RTW primarily experienced an ischemic stroke, had an average MRS score at onset of 3.1/4 (SD=1.5), and an MRS of 1.4 after 3 months (SD=1.1). They had anxiety and depression scores of 9.4 (SD=3.8) and 6.1 (SD=3.6), respectively (scores >11 indicate a mood disturbance), and FSSQ scores of 33.2/40 (SD=5.6). Patients that did not RTW had MRS scores at onset of 3.9 (ds=0.9) and MRS scores after 3 months of 2.3 (ds=1.2). Their anxiety and depression scores were 9.4 (ds=4.1) and 6.3 (ds=3.6), respectively, and they had FSSQ scores of 37.3/40 (ds=6.6). Data collection is ongoing and further analysis and comparisons will be completed when we have greater power.
Alternatives to Dental Amalgam

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Dental amalgam is a mercury containing alloy that is a commonly used dental material for the restoration of posterior teeth. Amalgam’s popularity can be attributed to its longevity, cost, and safety. It is currently the most cost effective method for the treatment of dental caries, and has been in use for over 150 years.

In postdoctoral clinics in the United States, the price of amalgam restorations ranges from $113-$207, while composites range from $129-$275. The WHO estimates that in Columbia it would cost over $936 million dollars annually to use composite resin and glass ionomer instead of amalgam. Current data shows that while alternatives to amalgam are available, they are not financially viable in many countries at this time.

Mercury releases to the environment from products that contain mercury, or processes that require mercury, can have a significant impact on human health. In 2009 the governing council of the United Nations Environment Programme (UNEP) reached a decision to convene an international negotiating committee (INC) to develop a global legally binding instrument regarding mercury. As a representative of the Pan American Health Organization (PAHO), I attended the fourth meeting of the INC in order to determine the implications a treaty on mercury would have on the availability and cost of dental amalgam.

Dental amalgam will likely be exempt from any ban on mercury products, as the FDA and WHO have both determined that it is safe for use in humans. However, international trade of amalgam, disposal of amalgam wastes, cleanup of sites contaminated by amalgam, and the education of patients on the risks of mercury toxicity are all issues addressed in the treaty that will influence the availability and cost of using dental amalgam in the future.

Although dental amalgam is safe for use in humans, amalgam wastes from dental clinics impact human health by contaminating pipes, water and soil. The best way to prevent mercury releases to the environment is to use alternatives to amalgam, however currently that is not a financially viable solution in many countries. Dentists can protect themselves, their patients, and the environment from mercury releases by following certain guidelines such as having a well-ventilated clinic, purchasing amalgam separators, disposing of mercury wastes properly, and buying pre encapsulated amalgam. By following these guidelines, dentists can significantly reduce mercury releases, while protecting themselves from any financial repercussions that may result from a future treaty regarding mercury.
Parent Presence on Morning Rounds in the Pediatric ICU: Perspectives of Parents and Providers

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Pediatric intensivists agree that communication with families plays a vital role in the care of critically ill children, but there is no consensus regarding the optimal means of communicating information to parents. In the last decade, the American Academy of Pediatrics and the American College of Critical Care Medicine have recommended adoption of “family-centered rounds” (FCRs), which incorporate parents into daily work rounds with the goal of improving communication and involving parents in decision-making.

Though FCRs have become widespread in pediatric settings, only a few studies have evaluated the practice. These studies reveal high levels of parental satisfaction with FCRs, whereas health care providers (HCPs) express varied opinions. Because little is known about the perspectives underlying these opinions, we sought to describe and compare parent and provider goals and expectations for FCRs.

We conducted a mixed-methods study investigating perspectives of parents and providers in the Medical/Surgical ICU (MSICU) at Children’s Hospital Boston. We conducted surveys of MSICU parents and health care providers, in-depth interviews of parents, and HCP focus groups. 100 parents and 131 HCPs completed surveys, and 21 parents and 24 HCPs participated in interviews and focus groups, respectively.

Survey data revealed significant differences between parents’ and providers’ perceptions of FCRs. While 92% of parents reported a desire to attend rounds, only 54% of HCPs preferred parental presence. There were significant differences in perceptions of parental understanding, with HCPs less likely to perceive that parents understood the format and content of rounds (p<0.001).

In interviews and focus groups, parents and HCPs alike expressed that parents should leave rounds with an understanding of their child’s status and plan for the day, with several parents emphasizing that this information should be provided in layman’s terms. There was disagreement, however, regarding the appropriate role of parents on rounds. Parents viewed rounds as a chance to ask questions and advocate for their child, and they expected transparency from the health care team, whereas HCPs felt rounds were not a time for in-depth discussion with parents. Providers stated that parental presence limited teaching and candid conversation and lengthened the duration of rounds.

As in previous studies, we found that parents report high levels of satisfaction with FCRs while HCPs express reservations; unlike previous studies, we also identified areas of incongruity between parent and provider goals and expectations that may contribute to these differences in satisfaction. These findings can inform implementation of faculty development around FCRs as well as improved parental preparation for FCRs, which may facilitate efficient use of time during rounds and better calibrate parent and provider goals and expectations.
Neural Predictors of Developmental Dyslexia in Pre-Reading Children: Imaging Manifestations of Genetic and Phenotypic Risk

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Developmental dyslexia (DD), characterized by disproportionate difficulty in reading compared to other cognitive abilities, is a prevalent learning disability among school-aged children. DD is thought to stem from specific deficits in mapping speech sounds onto their written counterparts (phonological processing, PP) and discriminating fast-changing speech sounds (rapid auditory processing, RAP). These skills depend on a cortical reading network; structural and functional changes within this network have been identified in adults and children diagnosed with dyslexia compared to typical readers. However, research has not yet addressed whether these differences are present or detectable prior to the onset of reading difficulty.

Using data from the first two years of the Boston Longitudinal Study of Dyslexia (BOLD study), we examined structural and functional brain differences (for PP and RAP) in pre-reading children at risk for dyslexia. Participants were enrolled in the study prior to starting kindergarten and followed up with structural and functional brain imaging and psychometric testing each year. To assess genetic risk, we examined differences between children with or without a family history of dyslexia (all children with a first degree relative with a clinical diagnosis were classified as family history positive). To assess phenotypic risk, we grouped children by later reading scores to explore whether baseline structural and functional brain characteristics could differentiate children who would develop into poor readers from those who would develop into typical readers.

Our results show that even before children learn to read, those with a family history of DD exhibit left hemispheric differences localized to the cortical language network in gray matter volume and functional activation during PP and RAP tasks. Specifically, these differences emerge in the left temporoparietal and occipitotemporal regions and the left fusiform gyrus. Children who develop into poor readers show similar differences prior to reading onset. These structural and functional differences persist from year 1 to year 2 of follow-up, and correspond to the neural differences that have been shown to differentiate adults/children with DD from typical-reading controls.

These findings reveal that neural changes associated with DD are manifest even before reading begins and persist after reading onset. Such changes could help identify children who may benefit from earlier reading interventions. While intervention strategies are most effective during kindergarten and first grade, DD is not reliably diagnosed until second or third grade. Therefore, early predictors of DD in pre-reading children are crucial for the development and improvement of early intervention programs.
Reengineering the Post-Discharge Visit within a Patient-Centered Medical Home

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Deficits in communication between inpatient and outpatient providers during transitions of care pose a threat to care continuity, patient safety, and patient satisfaction. The post-discharge visit represents an opportunity for providers to address communication deficits, perform medication reconciliation, and discuss patient self-care. However, many clinics lack a standardized post-discharge process, leading to redundancy in clinical workflow, inefficient use of resources, and frustration among patients and providers.

Brigham and Women’s Advanced Primary Care Associates, South Huntington is a patient-centered medical home (PCMH) in Jamaica Plain that serves adult patients from various backgrounds. The transitions of care team, led by an on-site nurse coordinator, aims to schedule post-discharge appointments within 72 hours of discharge. Daily one-hour sessions are reserved for post-discharge visits. Currently, the post-discharge visit lacks formal standardization.

First, an “as-is” process map was developed to understand workflow. Next, a cross-functional team, including a nurse care coordinator, on-site pharmacist, population manager, physician, and medical student, was formed to identify essential activities and potential areas for improvement. Through regular meetings the process map was improved to incorporate new ideas, insights, and patient perspectives.

The latest iteration of the process map was used to develop a PCMH post-discharge transitions checklist. The checklist incorporates many essential activities prior to, during, and after the post-discharge visit. Items were included if they were deemed critical by team members. A draft checklist has been incorporated into the electronic health record (EHR).

Overall, the use of process mapping to understand the current state of post-discharge planning has been instrumental to improving clinical workflow, and the checklist has been well-received by providers. Determining the “right” amount of improvisation versus standardization in the post-discharge environment has been tricky and involves multiple factors. Gathering essential and useful items for the checklist has been difficult because the difference between a task that can be standardized and a task that is specific to a single patient is often subtle. Lastly, choosing the minimum necessary items on the checklist has been challenging because too many checklist items opposes the inherent simplicity of the ideal, effective checklist.

In the future, we will improve the post-discharge process map and EHR checklist, contact “no-show” or complex patients to determine why they did not come to their post-discharge visits, design novel outreach mechanisms to reach “no-show” or complex patients, use the process map to design future interventions, and measure the use of the checklist as a process metric.
Long-Term Outcomes and Prognostic Factors in Locally Advanced Pancreatic Cancer Patients Undergoing Intraoperative Radiation Therapy

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Pancreatic adenocarcinoma is the fourth leading cause of cancer-related death in the United States, with a 5-year survival rate of only 6%. 30-40% of patients present with locally advanced pancreatic cancer (LAPC; surgically unresectable tumors that have not yet metastasized to distant sites). As surgery is the only potentially curative therapy, these patients especially need improved treatment protocols.

Since 1978, the standard of care at MGH has been to offer LAPC patients chemotherapy and/or external beam radiation therapy (EBRT) together with high-dose intraoperative electron beam radiation therapy (IORT). In 2005, Willett et al. published a retrospective analysis of outcomes for the first 150 IORT recipients at MGH, reporting a 7% long-term (>3 years) survival rate and a statistically significant inverse correlation between IORT treatment applicator diameter (a surrogate for tumor diameter) and overall survival.

Over the past decade, pre- and post-IORT chemotherapy have become more common for LAPC patients, and researchers have identified many new potential prognostic factors for overall survival in various stages of pancreatic cancer. Building on these developments, we conducted an expanded analysis of long-term outcomes and prognostic factors for overall survival for 194 consecutive LAPC patients who underwent IORT at MGH between 1978 and 2010. Using medical and public records, we characterized overall survival; the times and natures of local failure and distant metastasis; and potential demographics-, tumor-, and treatment-related prognostic factors for each patient. We then used univariate log-rank analysis to select prognostic factors to include in a final multivariate Cox proportional hazards model.

The mean and median overall survival times were 16.6 and 11.6 months. 1-, 2-, and 3-year survival rates were 48%, 15%, and 6%. Among the 183 patients with radiographic follow-up documentation, the overall local failure and distant metastasis rates were 36% and 56% respectively over a median follow-up period of 10.5 months. On univariate analysis, male sex, large treatment applicator diameter (>6 cm), and post-IORT chemotherapy use prior to local or distant failure were statistically significant predictors of overall survival at the p<0.05 level. Obesity (BMI>30) was borderline significant (p=0.06) at the univariate level. On multivariate analysis, only large treatment applicator diameter (HR=1.74) and post-IORT chemotherapy use (HR=0.59) remained statistically significantly associated with decreased overall survival. These results confirm the previously reported role of tumor diameter as a key prognostic factor in LAPC, but also suggest the importance of initiating chemotherapy shortly after IORT to improve LAPC survival outcomes.
Objective Monitoring of Insecticide Treated Bednet Adherence in Rural Uganda

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Background: Malaria kills nearly 800,000 people per year, most of whom are children under five years old living in Sub-Saharan Africa. Uganda has one of the highest malaria burdens in this region. Insecticide-treated bednets (ITNs) are the mainstay of malaria-prevention programs in Uganda, and through the help of local governments and the international aid community, bednet ownership in the country has risen from less than 20% in 2006 to approximately 50% in 2009. Yet despite reliance upon ITNs to prevent malaria, poor adherence and improper use pose major barriers to ITN efficacy. Surprisingly little is known about how ITNs are used, and no rigorous studies of ITN adherence have been carried out. This study aims to quantitatively characterize ITN compliance using a novel electronic adherence monitor, the SmartNet. SmartNet consists of a standard, WHO-approved ITN threaded with conductive fibers. These fibers are attached to a monitoring device that records conductance through the threads, indicating when the net is raised or lowered—a direct measure of net use.

Study Design: Thirty households in and around Kinoni, Mbarara District, Uganda, will be recruited to participate in a 3-month observational pilot study of the SmartNet device. During the study, we will examine SmartNet acceptability, functionality and reliability. Electronic reports of ITN adherence collected by the SmartNet will be compared to researcher visualization of net use and several participant self-report adherence scales. Correlations between these different adherence measures will be determined. We will also examine barriers to adherence through focused interviews with participants. Enrolment in the initial phase of the study—a series of focus group discussions about SmartNet acceptability—will begin in the fall of 2012.

Outcomes: We will present initial acceptability results.

Conclusions: We expect to demonstrate SmartNet acceptability and the feasibility of conducting large-scale trials with the SmartNet device in rural Uganda. We hypothesize that the SmartNet will record more non-use events that participant self-reports or researcher visualization. We will categorize barriers to adherence and explore socioeconomic predictors of adherence.
Regulation of Intestinal Stem Cells by LIN28/let-7

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The rapidly proliferating intestinal epithelium is an optimal environment for studying the regulation of somatic stem cells, which reside at the base of the crypts. The RNA-binding protein LIN28 is highly expressed in— and a critical regulator of— embryonic stem cells but is poorly characterized in somatic stem cells. LIN28A and LIN28B are paralogs that bind to and repress the let-7 microRNA, ultimately resulting in proliferation and pluripotency. This study investigates whether LIN28 is a key regulator of somatic stem cell populations by examining the intestinal epithelium under normal conditions, following injury and with ectopic overexpression of LIN28. Since LIN28 is pro-proliferative, it is expected to maintain stem cells under normal conditions and be upregulated during regeneration.

To identify whether LIN28A and LIN28B are present in the normal adult intestine, western blots, immunohistochemistry and QPCR for Lin28 mRNA were performed on mouse small intestine and colon. Regeneration was studied following chemical injury. Overexpression of Lin28a and LIN28B in the intestine using transgenic mice demonstrated that abnormally high amounts of their corresponding proteins reduce levels of mature let-7, as measured by QPCR, and alter intestinal epithelial histology.

LIN28A and LIN28B were undetectable by western blot and immunohistochemistry in adult mouse small intestine and colon. Lin28a mRNA was measured by QPCR, a more sensitive technique, at levels 1000x lower than in embryonic stem cells while Lin28b mRNA was undetectable. Lin28a mRNA was increased 3.9x from baseline following chemical injury. Although overexpression of Lin28a versus overexpression of LIN28B in transgenic mice caused similar repression of let-7, markedly different phenotypes resulted. Overexpression of Lin28a caused the crypts to expand, epithelial cells to lose differentiation and diarrheal illness to occur. Conversely, LIN28B overexpression did not cause crypt expansion, resulted in a different pattern of loss of differentiation and did not lead to acute illness.

Endogenous LIN28 was found in the highly proliferative adult intestine albeit at much lower levels than in embryonic stem cells and only as the LIN28A paralog. Lin28a upregulation following chemical injury provided further evidence of a role for LIN28 in gut homeostasis. It was also notable that ectopic overexpression of Lin28a had a greater phenotypic effect than overexpression of LIN28B even though LIN28A and LIN28B were shown to repress let-7 equally. Although LIN28 has classically acted primarily via repression of let-7, these results point to let-7 independent effects of LIN28, an area of current interest in the field.
Whole exome sequencing in a patient with uniparental disomy of chromosome 2 and a complex phenotype

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Whole exome sequencing and chromosomal microarrays are two powerful genetic technologies that have transformed the ability of researchers to search for potentially causal variants in human disease. These tools are increasingly being utilized in the clinical setting, leading to difficulty in the clinical interpretation of complex results. We present a prismatic case in which array CGH and whole exome sequencing were combined to search for causal genes in a complex patient found to have uniparental isodisomy of chromosome 2 (UPD2).

The subject of our study has a complex phenotype including skeletal and renal dysplasia, immune deficiencies, growth failure, retinal degeneration, and ovarian insufficiency. We explored multiple potential genetic etiologies of her phenotype, particularly those likely to result from UPD. A review of the literature on UPD of chromosome 2 suggested that the phenotype we observed was unlikely to be due to imprinting, and array CGH established that the patient had no large duplications or deletions. Thus, we hypothesized that the most likely genetic explanation of her phenotype was a rare, recessive variant on chromosome 2.

We performed whole exome sequencing which identified eighteen nonsynonymous, rare homozygous variants on chromosome 2. Additionally, we detected 12 potential compound heterozygous mutations on other chromosomes that could lead to a disease phenotype independent of the UPD found in this case. We described in detail several candidate variants in genes that could be causal in the phenotype, including one gene implicated in retinitis pigmentosa (FAM161A) and two genes with possible action in kidney structure and function (NAT8 and PLA2R1). We also noted that the patient had many features consistent with Bardet-Biedl syndrome and other related ciliopathies, and had several rare mutations in genes related to ciliary function. However, no single gene stood out as a likely candidate to follow up with functional analysis.

This study highlights the potential for detection of a large number of candidate genes using whole exome sequencing complicating interpretation in both the research and clinical settings. Forums must be created for publication and sharing of detailed phenotypic and genotypic reports to facilitate further biological discoveries and clinical counseling.
Chronic respiratory disease in resource-limited settings is prevalent and difficult to treat as a result of repeat exposure to inhaled toxins, inadequate access to diagnostic medical equipment, pharmaceuticals and qualified medical personnel. Chronic Obstructive Pulmonary Disorder (COPD), a disabling combination of emphysema and chronic bronchitis, relies on spirometric lung function measurement for adequate clinical care. Because spirometers are unavailable and mobile phones are increasingly affordable in most of the developing world, this project developed a low cost spirometer prototype for the mobile phone called the “TeleSpiro.” The key contributions of this work are the design of a repeat-use, low cost, phone-powered prototype meeting developing world user requirements. Computational Fluid Dynamics (CFD) simulations of expired air flow and international spirometry standards were used to design and machine a custom respiratory tube. A microelectrical mechanical systems (MEMS) differential pressure sensor, dual humidity/pressure sensor, microcontroller and USB hardware were mounted on a custom printed circuit board for measurement of air flow in the respiratory tube. The custom embedded electronics were programmed to transmit data to and receive power directly from either a computer or smartphone without the use of batteries. Software was written to filter and extract respiratory cycles from the digitized data, and filtered pressure signal profiles were created for common incorrect spirometry maneuvers. Differential pressure signals from Telespiro showed robust, reproducible responses to the delivery of physiologic lung volumes. The designed device satisfied the stringent design criteria of resource-limited settings and is ready for trials and regulatory approval testing.
Shifting attitudes towards health disparities: The Office of Negro Health Work from 1932-1951

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Despite the continued effort to mitigate health disparities in the United States, little historical research has been done analyzing the social, political and medical context surrounding past federal efforts to address health disparities and how this milieu contributed to the rise and fall of these efforts. In the early 20th century, the federal government first acknowledged and addressed the evidence-based existence of racial health disparities by forming the Office of Negro Health Work within the United States Public Health Service. This project aimed to contextualize and understand the attitudes about race, health, health disparities and justice among the communities that supported the formation and subsequent dissolution of this office over the course of its 20-year existence.

In order to characterize the changing attitudes and explanation of health disparities of the early 20th century, this study analyzes the divergent yet intersecting public health, medical and African American perspectives on race and health from this period. Sources included the publications of the Office of Negro Health as well as mainstream publications from popular medical journals and insurance companies, and reports from the United States Public Health Services that were referenced or saved in the archives of the National Negro Health Week located in the Tuskegee University Archives Repository. The Journal of the National Medical Association provided a more complete picture of the dissenting perspectives of African American physician-leaders of the era.

The rise and fall of the Office of Negro Health Work reflected the impact that attitudes towards race, changing approaches to civil rights, and the shifting burden of disease had on health policy over the course of its 20-year existence. The shift in the burden of disease in the US from infectious diseases with high mortality to chronic disease and much improved life expectancy, as well as the growing power of the medical establishment over the public health establishment and changing attitudes on explanations of health disparities not only set the stage for the formation of a minority health office, but also led to its eventual dissolution. Not until the 1980s would the country see a need for federal efforts aimed specifically at addressing the gross racial health disparities that continue to exist in the United States today. The story of the Office of Negro Health Works exemplifies the need to understand the way we as a society define race and illness, and conceive of the social determinants of disease.
Improvement in Medication Safety in Wockhardt Hospital, Nagpur

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Wockhardt Hospital is a private network hospital in Nagpur, India. In July 2011, Wockhardt commenced a quality initiative to ensure the organization was providing patients with the highest standard of care. Medication management safety is one of their primary areas of focus for improvement. To reduce medication errors and improve patient safety, Wockhardt Hospitals commissioned an audit of the medication process during a three week period in July, 2012.

The current medication management protocol involves nursing staff, physicians (consultants and resident medical officers (RMOs)), and pharmacy staff. Prescriptions are ordered by consultants, transcribed by RMOs, submitted by nursing staff, filled and delivered by the pharmacy, and administered and monitored by nursing staff. This audit was designed to inform hospital administration and staff of possible points of weakness in the medication process where errors may likely occur. Using the current medication safety Standard Operating Protocol (SOP) as a guide, the medication management process was traced from prescribing to administration via the tracer methodology. The process as written in the SOP was compared to the process observed via the audit, as well as to best practices for medication safety. Tracing the medication flow within the hospital allowed for the identification of possible points of weakness, and recommendations for improvement were made based on the qualitative observational analysis. These recommendations were presented to hospital administration and all the head nurses, and were implemented immediately. Recommendations included signing treatment sheets immediately after administering medications, checking medication deliveries before signing for the delivery, labeling all infusions with patient identifiers, complete medication name, and dilution, and preparing medications as they are to be administered.

During the audit, data was also collected about reported medication errors, including the unit where the error occurred, the severity of the error, related patient outcome, and subsequent action taken. These data were used in conjunction with the audit to pinpoint possible points of error in the hospital’s medication delivery process. The data will be qualitatively analyzed, and used as a benchmark to determine if medication errors were reduced following implementation of the recommended process improvements made as a result of the audit.

Medication management is an important factor of patient safety. Wockhardt Nagpur’s submission for their quality improvement initiatives was voluntary to continue advancing the level of patient care provided. This study was performed as part of an effort to improve quality by improving medication safety and reducing medication errors.
Technological innovations in medication packaging to improve patient adherence: a systematic review

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Background: Patient non-adherence to essential prescription medications has become one of our nation's largest public health burdens, contributing to approximately 125,000 deaths, roughly twice that of diabetes, and $300 billion in costs per year. Interventions intended to improve adherence have been directed at patients, physicians, and pharmacists, with varying degrees of success. One promising recent development has been electronic medication packaging for pill bottles, which can automatically track pharmaceutical product use and even feed data back to the physician, but little is known about the overall effectiveness of this tool in improving adherence.

Methods: We conducted a systematic review of peer-reviewed research testing the effectiveness of electronic medication packaging systems intended to improve medication adherence. We identified such studies by conducting Boolean searches of the MEDLINE, EMBASE, PsycINFO, CINAHL, and International Pharmaceutical Abstracts databases from 1948-2012. We selected all articles reporting studies in which a technological medication packaging system was investigated using randomized, controlled, prospective, or retrospective study designs. Studies that did not report medication adherence results were excluded. We extracted the results describing the impact of the intervention on adherence, and we also extracted any other key findings including changes in health status, costs, and participant feedback. Included studies were divided into two categories. Simple interventions only involved electronic packaging, and the device only interacted with the user and not the providers. Complex interventions combined electronic packaging with other interventions or transmitted the adherence data to a provider. These two categories of intervention were analyzed separately.

Results: Among 9,102 potential articles, 41 met inclusion criteria, describing 37 unique interventions. We found 11 simple interventions and 26 studies of complex interventions. Five out of the 11 simple interventions found that the intervention had a significant effect on improving medication adherence, as did 17 of the 26 complex interventions. Successful interventions generally provided the patients with feedback on their adherence rates, suggesting this is a critical component of an electronic medication packaging system. Positive participant feedback on devices was also associated with the successful interventions.

Conclusion: Electronic medication packaging is a promising intervention to improve adherence. Predictors of successful interventions include: making electronic medication packaging part of a complex adherence intervention; providing the patients with their adherence data through feedback; and using a device that has favorable post-intervention ratings by patients.
A Biomechanical Evaluation of the Sequent Meniscal Repair Device

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Menisci are fibrocartilaginous C-shaped cartilages in the knee joint, located between the tibial plateau and femoral condyles, which provide structural integrity and cushioning to the knee when it undergoes tension and torsion. Meniscal tears cause significant knee pain and swelling and may result in premature knee osteoarthritis. Therefore, torn meniscal tissue is repaired whenever possible. An inside-out suture repair is the gold standard for meniscal repair. This technique involves placing sutures into the knee using a needle through a cannula and tying the suture from the outside in. However, this suture-based method is associated with increased injury to neurovascular structures and perioperative morbidity. These limitations have given rise to the development of all-inside meniscal repair devices that allow sutures to be anchored from inside the knee, without passing needles through skin. While older all-inside devices such as the Ultra FasT-Fix were designed for simple suture repairs of torn meniscal tissue (a single vertical or horizontal stitch), newer devices, such as the Sequent Meniscal Repair, allow for the application of a series of running sutures.

In order to assess the quality of each meniscal repair technique, we compared the Ultra FasT-Fix and Sequent Meniscal Repair techniques to the current gold standard technique, the inside-out repair (No. 0 Hi-Fi). Paired (medial and lateral), fresh frozen porcine menisci were randomly assigned to one of three groups: Sequent Meniscal Repair (n = 10), Ultra FasT-Fix (n = 10) and No. 0 Hi-Fi inside-out repair (n = 10). Vertical bucket-handle tears were created in each of the menisci. Using the Sequent Meniscal Repair device, two vertical running stitches were placed in the midpoint of the pars intermedia. Likewise, two single vertical mattress sutures were placed with the Ultra FasT-Fix device or in a Hi-Fi No. 0 mediated inside out repair technique. Once repaired, the bucket-handle tear was completed through the anterior and posterior horns.

The menisci were fixed in custom made clamps aligned perpendicular to the tear and mounted in an Instron 8511 mechanical testing system. Cyclic loading was performed between 5 and 20 N at a frequency of 1 Hz. Displacement measurements (gap formation) were collected using the LabView 2011 program at an initial load of 5 N and after cycles 1, 100, 300 and 500. Load-to-failure testing was then performed at a rate of 3.15 mm/s, and the stiffness was calculated as the slope of the linear segment in each repair’s load-displacement curve.
Successful management of maxillofacial lesions generally follows a specific clinical course: full history and physical exam, radiographic analysis, accurate provisional diagnostic biopsy, surgical treatment, and definitive diagnosis (from resection specimen). Incisional biopsy is accepted by most clinicians as a dependable way of diagnosing the nature of oral lesions. Clinicians construct the treatment plans for oral lesions based on the incisional biopsy results. If resection of an entire lesion is the appropriate treatment, then the resection specimen of the entire lesion is sent to pathologists and a definitive diagnosis is rendered.

The diagnostic accuracy of incisional biopsy is still not well understood and yet despite this, it is accepted as the most reliable way to obtain a diagnosis for head and neck lesions. We hypothesize that the diagnostic accuracy for incisional biopsies from a heterogeneous series of oral lesions (mucosal, intrabony, glandular, other) will be 70% or higher based on a previous study looking at diagnostic accuracies of incisional biopsies for intrabony head and neck lesions only.

To test our hypothesis, we determined the concordance rate between incisional biopsy and final resection specimen for a variety of oral lesions through retrospective analysis of the Massachusetts General Hospital Oral and Maxillofacial Surgery patient 2005-2012 database. Patients who had undergone both incisional tissue biopsy followed by a definitive resection (n=285) were included in our study. Two hundred and forty cases (84.2%) were concordant when comparing the incisional biopsy and final resection pathology report diagnoses. The remaining forty-five (15.8%) misdiagnosed incisional biopsy cases were further analyzed to better determine the reasons why correct diagnoses were not rendered. Twenty-five of the misdiagnosed cases (55.6%) were intrabony lesions, seventeen cases (37.8%) were mucosal, 2 cases were (4.4%) were glandular lesions, and one case (2.2%) was of lymph origin. Specific reasons for misdiagnoses will be descriptively determined by Dr. Sadow, an experienced head and neck pathologist at Massachusetts General Hospital.

The data collected indicate an 84.2% (±4.2%) diagnostic accuracy for incisional biopsies. Further analysis still needs to be done on determining the reasons why a correct diagnoses was not rendered for the discordant cases. Dr. Sadow, Dr. August, and I hope to review the pathology for each discordant case and categorize the reason of misdiagnosis as either a sampling error, artifact of the histological slides, inadequate amount of tissue from biopsy, presence of inflammation, or pathologist error.
A novel syndrome caused by the E410K substitution in the neuron-specific protein β-tubulin isotype 3

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The microtubule cytoskeleton is essential for many cellular functions in the mammalian nervous system, including establishment of cellular morphology, neuronal migration, and development and maintenance of axonal and dendritic processes. Mutations in their component proteins, α- and β-tubulin, can perturb these processes and cause neurologic disease.

A certain set of missense mutations in TUBB3, the gene that encodes the neuron-specific β-tubulin isotype 3 (TUBB3), causes congenital fibrosis of the extraocular muscles type 3 (CFEOM3), a rare ocular motility disorder that results from aberrant growth of ocular motor neurons. Individuals harboring these TUBB3 mutations may have CFEOM3 in isolation or with other stereotyped neurologic findings suggestive of perturbed axon guidance.

To investigate the pathogenesis of these TUBB3-related disorders of axon guidance, we obtained detailed clinical and neuroimaging data for individuals who harbor one of the TUBB3 mutations that cause severe CFEOM3 (C.1228G>A, predicted E410K substitution). We found that these individuals have specific abnormalities in cranial and central axon guidance that cause a new genetic syndrome we now call the “TUBB3 E410K syndrome.” The syndrome consists of the congenital findings of CFEOM3 with facial weakness, Kallmann Syndrome, cyclic vomiting, and intellectual disability, as well as progressive peripheral neuropathy. We then generated mouse models to elucidate disease pathogenesis. Our preliminary results show that in mice, the Tubb3 E410K substitution, but not Tubb3 loss, causes axon guidance deficits that phenocopy human disease. These data suggest that that the TUBB3 E410K substitution causes disease in a dominant negative manner by disrupting specific processes in neuronal development or maintenance, and that particular subsets of cells are selectively vulnerable to perturbations in TUBB3 function.
Differential estrogen receptor signaling in normal mammary epithelial cells, primary breast cancers and metastases

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The estrogen receptor (ER) is expressed in ≈70% of sporadic breast cancer and activates genes driving cell proliferation and tumorigenesis. We have previously performed genome-wide analysis of ER binding sites in MCF-7 breast cancer cells and identified distinct mechanisms of tumorigenic ER signaling. Using EpCAM and CD49f as markers to enrich for ER-positive (ER+) cells obtained from primary non-malignant breast tissue, we seek to elucidate differences in ER signaling between normal and primary and metastatic ER+ breast cancer cells.

Viable breast epithelial cells were obtained from patients undergoing reduction mammoplasties, and ER+ breast cancer cells from primary tumors and metastatic effusions. Following dissociation into single cells, EpCAM+ cell subpopulations were isolated and stimulated with estradiol. Gene expression microarray analysis, chromatin immunoprecipitation and DNA sequencing (ChIP-seq) on transcription factors and histone modifications as well as DNAse I hypersensitivity assays (DHS) were performed, and compared to MCF-7 breast cancer cells.

Triplicates of normal, ER+ breast cancers, and metastatic ER+ cancer were analyzed. Gene expression profiles revealed differences in estradiol regulated genes between primary normal, breast tumor, and metastatic ER+ breast cancer cells. Genes that promote cell cycling and cell proliferation were downregulated in non-malignant tissue but were upregulated in breast cancer cells. Our ChIP-seq results showed differential binding of ER between normal and ER+ breast cancer with little common overlap, and motif analysis of these binding sites demonstrated the enrichment of ERE motifs in common sites, TCF12 motifs in unique normal sites, and FOXA1 motifs in unique breast cancer sites. Analyses of the distribution of histone modifications and DHS regions demonstrated distinct patterns at shared, normal, and breast cancer ER binding sites, suggesting functionality and further validating differential ER binding.

There are contrasting differences in ER signaling between normal mammary and ER+ breast cancer cells, with estrogen appearing to have anti-proliferative effects in normal luminal cells compared to pro-proliferative effects in BC. ER ChIP-seq has identified unique motifs, distribution of histone modifications, and DHS regions specific to unique normal, cancer and shared ER binding sites. Our studies point to TCF12 as a potential ER pioneer cofactor in non-malignant breast tissue and provide more data in support of FOXA1 as an important ER coregulator in ER+ breast cancer. Our data provides evidence for key alterations in ER-signaling during tumorigenesis and could lead to the identification of novel strategies to target breast cancer specific ER signaling.
Role of Transcription Factor KLF2 in Lineage Specification of hiPSC-derived Hematopoietic Stem Cell Progenitors

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Approximately 60,000 hematopoietic stem cell (HSC) transplantations are performed worldwide each year. Despite sourcing HSCs from bone marrow, mobilized peripheral blood, and umbilical cord blood, clinical use remains limited by supply of HSCs. Advances in induced pluripotent stem cell (iPSC) technology opened the possibility of growing autologous HSCs from a patient’s own somatic cells (e.g., fibroblasts), offering a potential solution to graft-versus-host disease.

Recent studies have revealed that definitive hematopoiesis, the major contributor to the permanent, adult hematopoietic system, originates at least in part from the aorta-gonad-mesonephros (AGM) region during embryonic development. Specifically, it has been observed that hemangioblasts give rise to HSC progenitors through a hemogenic endothelial cell intermediate. Furthermore, our laboratory and others have demonstrated that upon initiation of heartbeat, blood flow in the developing embryo promotes hematopoiesis from endothelial precursors. Recently, transcription factor KLF2 has been identified as an integrator of endothelial cell response to flow, and KLF2 expression has been shown sufficient to trigger many flow-dependent endothelial phenotypes. Interestingly, KLF2 expression is upregulated by flow in hematopoietic precursors of the AGM region. Therefore, we propose KLF2 expression is critical for the shear stress-mediated signaling that stimulates hemogenic endothelium-to-HSC progenitor transition. Specifically, we hypothesized that forcing expression of KLF2 in hiPSC-derived endothelial cells will induce formation of HSC progenitors.

To test this hypothesis, embryoid bodies (EBs) were cultured from human iPSCs. VE-Cadherin+ cells were isolated from day 8 EBs by magnetic bead sorting, plated, and transduced with adenovirus containing KLF2 or control GFP constructs. KLF2 expression was measured by qRT-PCR. FACS was used to evaluate number of CD41+ HSC progenitors. Colony forming unit (CFU) assay was used to evaluate the number and type of colony forming HSC progenitors.

qRT-PCR confirmed successful infection of VE-Cadherin+ cells using adenoviral vectors as documented by increased expression of KLF2 in the ad-KLF2 sample compared to ad-GFP control. Preliminary CFU assay data suggests no significant difference in total number of colony forming progenitors between ad-KLF2 and ad-GFP samples. However, increased expression of KLF2 promoted a slight enhancement towards the erythroid fate – a result consistent with previous studies showing abnormal development of erythroid cells in KLF2−/− mouse embryos. Additional dosage experiments are necessary to evaluate the impact of KLF2 upregulation on number and specification of HSC progenitors. Understanding this mechanism will help elucidate molecular control of blood cell lineage specification and aid in the design of future stem cell-derived blood cell therapeutic interventions.
Predictors of Pain in Juvenile Idiopathic Arthritis

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Juvenile Idiopathic Arthritis (JIA) is characterized by inflammation of the joints resulting in stiffness and pain. In the absence of standardized methods of pain assessment in JIA, little is known about the relationship between arthritis severity and perceived pain. The aim of this pilot study is to determine the extent to which markers of arthritis severity, systemic inflammation, functional disability, sensory function and psychological state correlate with pain in JIA.

Following local IRB approval and written informed assent/consent, 100 children aged 7-17 years who have been diagnosed with JIA will be recruited from the Rheumatology Clinic at Boston Children’s Hospital. Markers of disease severity will be assessed during routine clinical examination, including patient and physician global assessment, number of joints with active arthritis and number of joints with limited range of motion. Routine laboratory tests will measure markers of inflammation (erythrocyte sedimentation rate and c-reactive protein). Sensory function will be assessed using Quantitative Sensory Testing (QST) at three skin sites on the hand: (i) inflamed joint, (ii) non-inflamed control joint, and (iii) non-inflamed, non-joint control. Cold and heat detection and pain thresholds will be tested using a Peltier thermode. Mechanical touch detection and pain threshold will be tested using von Frey filaments, vibration sensation with a vibrometer, allodynia using a brush, and pressure pain threshold using an algometer. Patients will work with their parents to fill in a series of 6 standardized surveys to assess 1) pain intensity (scored 0-10 on Visual Analogue Scale); 2) functional ability (Functional Disability Index and Childhood Health Assessment Questionnaire); and 3) mental health status (Pediatric Symptoms Checklist, Pediatric Pain Catastrophizing Scale, and the State Trait Anxiety Inventory).

Study design and QST training have been completed and patient recruitment will commence in September 2012. This is a pilot study seeking to acquire cross sectional patient data at a single point in time. We anticipate proceeding with longitudinal studies in order to further elucidate the etiology and evolution of chronic pain in JIA. Ultimately, the goal is to identify biomarkers, including measures of disease severity, sensory abnormalities, and psychological factors, which correlate with contributors to patients’ pain. This, in turn, will allow analgesic and anti-inflammatory therapies to be optimized for individual patients.
Serum markers of immune activation in HIV-1 subtype C infected adults

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Comprehensive studies of adults with incomplete immune reconstitution despite suppressive Highly Active Anti-Retroviral Therapy (HAART) show that phenotypic indices of systemic translocation of microbial products and the subsequent T-cell immune activation distinguish failed from successful immune reconstitution. In treated children, the determinants of immune activation are poorly understood. We hypothesize that the baseline levels of immune activation and indicators of bacterial translocation will predict CD4+ T-Cell recovery and viral load suppression in HIV-1 infected children.

Lipopolysaccharide ELISA is the experimental gold standard in studying immune activation secondary to gut microbial translocation. However, acquisition of appropriate samples requires fasting, hence it is not practical to conduct such studies using a pediatric cohort. We conducted a cross-sectional study of serum markers of immune activation in 30 HIV-1 infected treatment-naive adults (median CD4 T-cell count: 251.5, IQR 45-532; median HIV viral load 82483, IQR 14353-224003) to select the best marker for studying immune activation in children. We employed the ELISA assay to investigate correlations between serum markers and outcome measures of HIV disease progression (Viral load and Absolute CD4+ T-Cell count).

We selected five serum markers; Endotoxin core antibodies (endocab), CD14, CD163, Intestinal Fatty Acid Binding Protein (iFABP), and Interleukin-6. The endocab assay is an indirect measure of serum lipopolysaccharide levels. An increase in endotoxin is associated with a decrease in the baseline level of endotoxin core antibodies. Soluble CD14 is a glycoprotein that mediates the interaction of lipopolysaccharide with cells, and signals the presence of gram-negative bacteria. Soluble CD163 is cleaved from the CD163 membrane protein and reflects states of activation and proliferation of macrophages during inflammation. iFABP is a cytoplasmic protein that binds long chain fatty acids and is specifically localized in the epithelium cells of the small bowel. A rise in iFABP serum levels is indicative of intestinal cell damage. Interleukin-6 is a cytokine expressed during acute inflammation and reflects T-cell activation.

Our results show that Interleukin-6 and soluble CD14 had significant negative correlation with absolute CD4+ T-Cell count (p <0.05; Spearman correlation). Endocab, soluble CD163 and iFABP did not show significant correlations with absolute T cell counts. We did not observe statistically significant correlations between any of the five markers with HIV-1 viral load in this pilot study. Based on our data Interleukin-6 and soluble CD14 have the best correlation with clinical findings and hence show the most promise for the study of immune activation in children following HAART.
Defining and Measuring Mindfulness

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Much research has been done on the clinical benefits on mindfulness, or meta-awareness of the present moment experience. This research indicates that mindfulness training can reduce anxiety, depression, and pain, increase immune function, and alter brain activity.

To date, there is no gold-standard test to measure mindfulness and the available tests utilize self-report and have psychometric issues. The long-term goal of this multi-phase project is to develop an objective tool to measure mindfulness.

We hypothesize that analysis of “stream of consciousness” texts generated by subjects while they look at an image will reveal subjects’ meta-awareness, which, once qualified and quantified, can provide a more objective way to measure mindfulness.

The goals of the first phase are to 1) identify pictures and develop instructions that best elicit examples of meta-awareness, 2) develop a coding scheme to analyze the texts, and 3) explore the relationship between the number of instances of meta-awareness in text and years of meditation experience.

We tested 6 pictures (2 positive, 2 negative and 2 neutral) and 2 sets of instructions on 12 subjects with mindfulness experience. Each subject was given one set of instructions and 3 pictures, one of each valence. Subjects had 5 minutes per picture to type everything that came to mind. Coding categories were then generated from the 36 writing samples.

In general, subjects exhibit more meta-awareness when writing about positive or negative pictures. Subjects with more examples of meta-awareness in negative and neutral pictures averaged more years of meditation experience than those with the lowest meta-awareness score for the same pictures. No similar correlation was found for positive pictures, thus making negative and neutral pictures a better choice for future use. A median split indicated that the 6 subjects with highest meta-awareness score averaged 21.8 years of meditation experience whereas the 6 subjects with least meta-awareness score averaged 13.3 years of experience.

Regarding the instructions, subjects wrote many more examples of meta-awareness when given more elaborate instructions, but only when viewing positive images. Since the more elaborate instructions give examples of what subjects can write about and thus introduce more response bias, we will use the shorter instructions.

While our study sample size precludes proper statistical analysis, this project establishes the foundation upon which subsequent phases will be built.
Caregiver-reported unmet needs and impact of social context on families caring for medically-complex children

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Families caring for medically-complex children often face significant financial and social challenges in addition to high medical demands, but there is limited data about how these factors impact families. This study aimed to assess caregiver-reported psychosocial challenges and unmet needs of families caring for medically-complex children, and understand how these factors impact caregiver burden.

Over a 3 month period, caregivers of 104 medically-complex children completed a written 41-item survey about their child’s medical and functional status, social context, and unmet needs during a primary care visit. Data analysis used chi-square tests for categorical variables and t-tests for continuous variables.

91.3% of caregivers reported unmet needs in at least one of seven areas screened (mean 2.84). Families reported greatest unmet needs for home caregivers (62.6%), recreational and social opportunities (59.0%), mental health services (55.4%), and supportive therapies (55.1%). Unmet needs for medical supplies (30.6%) and equipment (29.6%) were less frequently reported. Number of unmet needs was positively associated with caregiver's rating of child's medical severity (p=0.005), degree of difficulty in coordinating care (p<0.001), and time spent worrying about the patient’s health (p=0.001) and impact on siblings (p=0.001). Caregivers who felt their child had a personal doctor reported fewer areas of unmet needs (2.61 vs. 3.71, p=0.034). More unmet needs were reported if an adult was unable to work due to the child's medical condition (3.41 vs. 2.21, p=0.002). Caregivers reported high levels of social vulnerability, with 33% having only 1 adult in the home capable of caring for the child, 39.4% receiving food stamps, and 30% worrying at least monthly about money for necessities. Resource instability was positively associated with monthly admissions (p=0.027) and caregiver rating of condition severity (p=0.041), but was not associated with level of developmental delays.

Families caring for medically-complex children report remarkably high levels of unmet needs, particularly for non-medical services, and describe significant social vulnerabilities that impact medical care and caregiver burden. These findings support the need for proactive psychosocial screening and caregiver support for families with medically-complex children within the Medical Home.
Barriers to Preventive Cancer Screening in a Cohort of Transgender Patients Accessing Services at an Urban Community Health Center

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Regular preventive screening decreases the morbidity and mortality associated with gynecological cancers. Cancers associated with female natal reproductive structures, including the cervix, uterus, ovaries, and breasts, have been documented in transgender patients. Although recommendations for preventive screening for cervical and breast cancer in transgender patients exist, no formal studies have been performed that document the actual rates of mammography and pap smears used to detect precancerous cervical cells in this population or that explore the barriers to compliance with existing recommendations.

We performed a qualitative, retrospective chart review of the medical record data of a sampling of approximately 100 of the 700-patient cohort of all transgender patients who sought primary care services at Fenway Health over a 6-year period (2006-2011). Data about relevant client histories and female reproductive organ screening, including pap smears and mammograms as well as their associated cytology and pathology reports, were collected from the medical record.

The transgender patients sampled disproportionately exhibited histories of emotional, physical and sexual abuse as well as mental health diagnoses, such as depression, generalized anxiety, and PTSD, and risk factors such as suicidality and self-harm. Lack of health insurance, difficulties finding and retaining gainful employment, and inability to finance medical care were also common among this population. It was also observed that disparities in consistent preventive screening reminders to patients exist both across providers and across patients of individual providers.

We found a variety of reasons to explain the preventive screening disparity faced by transgender patients. The lasting effects of trauma may hinder patient compliance with clinician recommendations and treatment plans. The invasive procedures involved in the screening of organs tied to those histories of trauma may be emotionally triggering for patients and may hinder patient desire for these screenings. Financial constraints exacerbated by rejection from family and community and perceived employment and educational discrimination due to the transgender identity may further hinder regular screening in this cohort. The varying rates of provider recommendations for preventive cancer screenings may reflect provider oversight that can be attributed to focusing on the complex medical histories of this patient population to the exclusion of basic preventive care services. Standardized protocols for the delivery of cancer screening reminders for providers treating transgender patients are needed in order to combat the growing disparity seen in this community in regards to its preventive screening needs.
Curricular Changes to Expand the Health Care Roles of Orthodontists as "Oral Physicians"

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Oral health is directly related to overall, systemic health. As over 100 diseases manifest in the oral and craniofacial region, early detection of such diseases will be beneficial in the treatment or etiology of both oral and systemic disease. Maximizing the opportunity to detect and assess chronic systemic diseases during dental visits will require a change in the dental curriculum to train dentists, specifically orthodontists, as oral physicians. Orthodontists usually see their young patients once a month for two years, putting them in a position to assess overall growth, development, and health during the most formative years.

The objective of this study was to determine orthodontists’ willingness to be trained to function as oral physicians, providing limited primary preventive care. The specific aims were to determine: the willingness of orthodontists to function as oral physicians; whether they would need more training; and their willingness to obtain additional training. It was hypothesized that the outcome would be affirmative for all three specific aims.

An online questionnaire was developed, pretested, and distributed electronically to 20 orthodontic faculty, 26 orthodontic residents, and 65 fourth year dental students at the University of Illinois at Chicago College of Dentistry. It contained 40 questions about knowledge and attitudes regarding expanded roles for orthodontists, including recognition and/or referral for developmental and eating disorders, mental health and behavior issues including ADHD, autism spectrum disorders, addiction, and substance abuse. Participation was voluntary.

Of the 40 respondents, 37.5% were orthodontic faculty, 35.0% were fourth year dental students, and 27.5% were orthodontic residents. More dental students and faculty were willing to function as oral physicians, compared to residents (71.4%, 60.0%, 33.3%, respectively). Fisher's Exact test indicated that more fourth year dental students and faculty were willing to receive additional training to expand their knowledge to manage systemic diseases compared to orthodontic residents (100% compared to 62.5%; p value 0.049).

Senior dental students and orthodontic faculty appear to be potentially interested in expansion of orthodontists’ duties to include function as oral physicians. Before changes can occur, the dental faculty, current and future dentists, public, licensing authorities, and other stakeholders need to support the concept of dentists as oral physicians. The results of this study will become the basis for developing a national survey of orthodontic program directors, faculty, and students to suggest an appropriate potential curriculum for training orthodontists to function as oral physicians.
Associations Between Preoperative Functional Status and Functional Outcomes for Joint Replacements in the Dominican Republic

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**Background:** In developed countries, patients undergoing total joint replacement (TJR) with lower preoperative function improve more functionally than patients with higher preoperative function but the lower functioning preoperative patients ultimately have worse functional status scores following TJR. This information has informed optimal TJR timing in developed countries. It is currently unknown if similar correlations exist in developing countries.

**Methods:** Patients undergoing total hip or knee replacement in the Dominican Republic completed WOMAC and SF-36 surveys preoperatively and at 12-month follow-up. Patients were stratified into low, medium, and high scoring preoperative groups based on their preoperative WOMAC function scores (possible range 0-100 with 100=best). The stratified groups’ improvement scores and outcome scores at 12-month follow-up were compared using ANOVA models that adjusted for demographic differences.

**Results:** Patients with the worst preoperative function scores made the greatest gains in function (76.2 point improvement [SD: 14.9] for lowest scoring preoperative tertile as compared with 29.2 point improvement [SD: 19.5] for highest scoring preoperative tertile) following their TJRs (P<.001). However, there was no significant difference in pain or function at 12-month follow-up between patients who scored low (final WOMAC score=86.2, SD:11.9) and high (final WOMAC score=90.0, SD:11.8 ) preoperatively (P=0.065).

**Conclusion:** Patients with the worse preoperative function gained the most following TJR (consistent with research from developed countries) but achieved similar scores 12 months after surgery. This finding contrasts observations in developed countries that the lower scoring preoperative groups do not catch up to those with better preoperative function. These results should be confirmed; they suggest that in developing countries waiting longer to offer TJR may optimize improvement from the TJR without threatening the functional outcome.
The measurement of cardiac output (CO) during labor and delivery has historically required invasive monitors, but these are rarely used in gravid patients. The Electric Cardiometry (EC) device, ICON, is a noninvasive method of determining CO. Thus far, the ICON device has not been used to evaluate hemodynamic changes in laboring patients. The purpose of this study is: 1) Use the ICON device to measure CO trends noninvasively in a modern cohort of laboring patients and, 2) Determine the changes in hemodynamic parameters among patients receiving epidural vs. CSE. This is a randomized control trial of healthy term patients who elected regional analgesia for labor. Patients were randomized to either epidural of CSE for regional analgesia. The ICON was used to determine hemodynamic parameters: heart rate (HR), stroke volume (SV), cardiac output (CO), mean arterial pressure (MAP), systolic and diastolic blood pressure (SBP, DBP), and stroke volume variation (SVV).

Twenty-two parturients completed the study, twelve parturients received epidural and ten received CSE analgesia. There was no statistically significant difference in either SBP or DBP between the two groups. Both groups showed a decrease in MAP at fifteen minutes after initiation of neuraxial analgesia. The CSE group displayed a significant decrease in CO at fifteen minutes after initiation and this significant decrease persisted until forty-five minutes following CSE and resolved at sixty minutes. There was a significant drop in HR at thirty minutes in both groups. This drop persisted up to sixty minutes in the CSE group. No differences in SV were noted between the groups. Four patients out of the twenty-two changed their fetal heart tracings from Category 1 to Category II within an hour after placement of neuraxial analgesia. Three out of four of these patients had received a CSE.

These preliminary results suggest that epidurals and CSEs present a similar hemodynamic profile when compared in terms of SBP and DBP changes. On the other hand, CO values show different trends in epidural versus CSE group. This drop in CO is most likely attributed to a drop in the HR and variability in SV. This is a significant finding that may affect uterine blood flow in patients receiving CSE and may account for possible fetal heart rate decelerations that have been observed following initiation of CSE. This study concluded that CSEs are associated with significant decrease in cardiac output as compared to epidural analgesia for labor.
Prevention, Health Awareness, and Choice through Education (PHACE)

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Prevention, Health Awareness, and Choice through Education (PHACE) is a valuable community service opportunity offered to first-year medical and dental students to serve as a reproductive health instructor for high-risk adolescents in the city of Boston. PHACE is a unique opportunity to discover urban health issues, learn how to teach in a middle/high school, understand the complexity of addressing sexual health topics among underserved teenagers, and develop mentoring skills for students with behavioral and learning deficits.

In the 2011-2013 cycle, we trained 12 PHACE instructors to teach important topics on sexual health and safety in 6 middle and high school classrooms, for a total student population of about 50 students. Our primary goal was to establish a safe teaching environment where students would feel comfortable and where they would be able to voice their concerns and questions on sexual health issues. Our secondary goals were to dispel inaccurate knowledge/myths about sexual health and to have our students retain at least one key piece of information from each lesson as a take-home or summative message.

We encouraged participation through games, skits, and quizzes to better engage the students and even championed a tutorial, discussion-based format in some of the classrooms. Game-based reviews of the subject material were most effective and favorable among the students. By the end of the curriculum, our students were aware of key, hot topic sexual health issues such as contraception methods, signs and symptoms of STDs, and safe sex practices.

This program allowed us to gain a deeper appreciation for the adversity faced by underserved populations, renew our passion for mentoring and teaching others, and obtain the self-satisfaction from making a difference in the lives and education of at-risk youth.
Safety and Effectiveness of Seprafilm at Cesarean Section

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Like other forms of surgical intervention, Cesarean Section can result in the formation of adhesions, with reported incidences ranging from 24-73%. This has prompted the adhesion barrier industry to aggressively market their products for use during cesarean delivery. While there is large evidence of one such adhesion barrier (Seprafilm) at preventing adhesion formation in general and gynecologic surgery, its efficacy and safety remain largely unexplored in the field of obstetric surgery. Thus, the purpose of our study is to evaluate the postoperative course, degree of future adhesive disease, and adhesion-related complications among patients in our hospital who received Seprafilm at cesarean delivery.

We designed an IRB-approved, retrospective cohort study to examine the effectiveness of Seprafilm. We included all patients undergoing a cesarean delivery at Brigham & Women’s Hospital between the years 2006-2010 who returned for a second surgical procedure. Control subjects were matched to the Seprafilm cohort on a 2:1 basis based on hysterotomy type, whether the initial surgery was a primary or repeat cesarean section, and the surgeon’s identity. For all subjects, we collected demographic data and relevant medical and surgical histories. Our primary outcome of interest was the presence, severity, and location of adhesions at the time of the patient’s second surgical procedure. Secondary outcomes of interest included adhesion-related complications or scar dehiscence at the second surgical procedure, and immediate infection with the index surgery.

There were 51 subjects who received Seprafilm at their index delivery and 102 controls. Seprafilm was placed more frequently in patients with black ethnicity (OR=2.8, 1.03-7.81) and those who had dense adhesions at index delivery (OR=2.5, 0.95-6.86). There was no statistically significant difference between the cohorts in terms of immediate infection, the formation of adhesions, or surgical times at follow-up. Seprafilm placement tended to show fewer dense adhesions among patients with adhesions at their index delivery, though the number of subjects was too small to show statistical significance (OR=0.53, 0.13-2.27). Those receiving Seprafilm had three times the rate of hysterotomy dehiscence at follow-up cesarean, but this outcome was also too rare to show significance. Thus, Seprafilm may have benefit if used as secondary prevention for adhesion formation, but its overall utility should be confirmed with randomized studies.
Prescriptions for opioid painkillers increased dramatically in the past 20 years, largely due to successful campaigning by patient advocacy groups, pain specialists, and pharmaceutical companies advocating more aggressive use of opioids in treating patients with chronic non-cancer pain. Pain specialists advocating for broader use of opioids in the early 1990s introduced "pain contracts," agreements between patients and physicians designed to address concerns about the medical and legal repercussions of possible iatrogenic addiction and diversion to illicit drug markets. Yet pain contracts and other measures have done little to curb the rise in morbidity and mortality related to opioid abuse; more than 15,000 people in the United Stated died in 2011 from prescription opioid overdoses, a more than three-fold increase since 1990. Among pain patient advocacy groups working to destigmatize and liberalize medical treatment for chronic pain, pain contracts were viewed with a mix of apprehension and acceptance; strict adherence to pain contracts could stigmatize and limit access to narcotics, but they could also help normalize such treatment by creating a symbolic legal framework specifying conditions for proper patient adherence. Pharmaceutical companies that manufactured opioids also recognized that pain contracts could be instrumental in countering "opiophobia" among patients and physicians. Companies like Purdue Pharma, the maker of the popular drug OxyContin, thus provided substantial financial support to patient advocacy groups, medical boards, and bioethics institutes that discussed and promoted pain contracts as part of a broader mission to increase sales by minimizing the risks of opioids while emphasizing their unrealized public health potential. This paper outlines the history of pain contracts to show how discourse surrounding their use helped legitimate novel and controversial clinical applications of opioids for chronic pain.
Measuring Cystic Fibrosis Mucus Viscosity using micro-Optical Coherence Tomography

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It is well established that the ion transport abnormalities affect mucus viscosity in cystic fibrosis (CF) afflicted airways. Investigation of mucus viscosity is therefore an active component of the research on the pathogenesis and treatment of CF. Past research has measured mucus viscosity using either bulk rheometers or microscopic fluorescent particle tracking. Our laboratory specializes in optical coherence tomography (OCT), an optical imaging modality that produces real-time cross-sectional microscopy based on interferometry measurements. Here we introduce a method for measuring viscosity using Micro-Optical Coherence Tomography (µOCT), our recently developed form of OCT that has sufficient resolution to track either exogenous beads or endogenous inclusions in the mucus.

Our µOCT technology is capable of visualizing particles as small as 500nm at high frame rates (40 fps). As in fluorescent particle tracking micro-rheology, dynamic viscosity is computed by measuring the mean squared displacement of particles in the mucus and applying the generalized Stokes-Einstein relationship. As the viscosity of the solution increases, the Brownian motion exhibited by particles in solution decreases. Particles are tracked using a standard centroid-locating algorithm.

We validated our methodology on dextran solutions of varying concentrations with exogenous 500nm beads, which yielded strong concordance with published data. Furthermore, we were able to locate and track native micron-scale particles in human mucus with sufficient accuracy to distinguish CF from wild type mucus based solely on viscosity. (p<.05, n=5) Preliminary results suggest that this method can be performed in the presence of transverse motion, such as that seen in mucus flow in vivo, by subtracting the bulk motion vector from all particle tracks.

Because endogenous particles can be used, µOCT rheology provides two key benefits over current fluorescent particle tracking methods. Our methodology both eliminates the potential for interactions between mucus and exogenous particles as a source of error and enables the measurement of viscosity in situations where addition of fluorescent beads is not feasible. In particular, the ability to measure viscosity using only endogenous particles allows for in vivo experiments to explore the importance of mucus viscosity changes in the in vivo pathogenesis of CF.
The Interaction of mTOR Signaling and Autophagy in Pancreatic Cancer

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Pancreatic cancer is a lethal malignancy that is generally not amenable to available therapies. In the United States alone, more than 34,000 deaths are a direct result of the disease, which has a 5 year survival rate of less than 5%. Partly underlying the aggressive and intractable clinical history of pancreatic cancer is its complex, heterogeneous biology. While pancreatic cancer cells have prototypical genetic abnormalities, such as dysregulation of the RAS signaling pathway, they also follow a unique metabolic pattern. One such metabolic distinction is its addiction to macroautophagy, which is a bulk, cytoplasmic process that recycles organelles. Autophagy is emerging as an attractive target for elucidating the basic biology of pancreatic cancer as well as developing effective therapies.

Recently, our lab completed a whole genome RNAi screen of a pancreatic ductal adenocarcinoma (PDAC) cell line, 8988T. We analyzed the screening data using a proprietary pathways analysis algorithm developed by Ingenuity Inc. Three of the top five pathways that were critical to PDAC survival and maintenance in vitro were related to or a component of the mammalian target of Rapamycin (mTOR) signaling pathway. mTOR is a serine/threonine kinase that senses and integrates extracellular signals such as nutrient intake and growth factors. Interestingly, mTOR is also known as a master regulator of autophagy. We hypothesized that the interaction between mTOR and autophagy can be exploited as a new avenue for developing treatments for pancreatic cancer.

In harmony with our present understanding of mTOR’s inhibitory regulation of autophagy, immunofluorescence studies show that Rapamycin significantly increased the presence of autophagosome puncta—a widely accepted proxy for autophagic activity—in pancreatic cancer cells expressing the LC3-GFP transgene. Additionally, Rapamycin increased autophagic flux, a dynamic measure of autophagic activity. Preliminary studies show that PDAC cells are sensitive to Rapamycin, an mTOR inhibitor, and previous data from the lab show that chloroquine, a late-autophagy inhibitor, significantly suppresses PDAC growth. Based on our preliminary results, we hypothesize that the concomitant inhibition of mTOR and autophagy decrease survival and growth of PDAC cells. We are currently investigating this potential synergy as well as the mechanism responsible for this increased susceptibility.
Insurance-Based Differences in Lower Extremity Elective Surgery Rates Before and After Healthcare Reform

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Background: The Supreme Court’s recent ruling to uphold the national healthcare mandate will increase the number of insured Americans through the development of subsidized healthcare plans and health insurance exchanges. While insurance-based differences in the rate of upper extremity elective orthopaedic surgery have been described before and after healthcare reform in Massachusetts, no comprehensive study has compared the rates of lower extremity elective surgery as a result of this change.

Methods: A retrospective review was performed within a department of orthopaedics at a tertiary-care, academic medical center in Massachusetts. The rate of elective lower extremity surgery performed before and after the healthcare reform (2005-2006 and 2007-2010, respectively) was calculated. The patients were categorized by insurance type (Commonwealth Care, Medicare, Medicaid, private insurance, Worker’s Compensation, TriCare and Uninsured). After adjusting for age, gender, and diagnosis, differences in rates of surgery (ROS) between the time periods and among insurance subgroups were calculated.

Results: The post-reform ROS (48.2%; 95% CI, 47.2% – 49.2%) was higher than the pre-reform ROS (41.9%; 95% CI, 40.2% – 43.5%).

When subdivided into three cohorts (Commonwealth Care, other-insured, and uninsured), a difference in pre- and post-reform ROS was identified in the other-insured subgroup.

While uninsured patients did not differ in ROS before (34.4%; 95% CI, 28.5% – 40.2%) and after reform (33.6%; 95% CI, 27.7% – 39.5%), other-insured patients had a greater ROS after the reform (48.6%; 95% CI, 47.2% – 49.2% vs. 42.5%; 95% CI, 40.7% – 44.2%).

For Commonwealth Care, the post-reform ROS (48.0%; 95% CI, 42.3% – 53.7%) was comparable to that of post-reform other-insured patients, greater than the post-reform ROS of uninsured patients, and less than post-reform Worker’s Compensation (73.2%, 95% CI, 68.2% – 78.3%).

Conclusion: Following healthcare reform, the rate of elective lower extremity orthopaedic surgery increased. This may be the effect of having more insured patients eligible to have surgery. However, the causality between insurance status and ROS has not been established. Therefore, this study may inform future investigation into the effects of healthcare reform on rates of elective surgery at both the state and national levels.
Validating the Use of Amniotic Mesenchymal Stem Cells in Wound Healing

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Background/Purpose: Wound healing, a complex process involving the migration and proliferation of cells and the deposition and remodeling of new extracellular matrix in response to injury, often results in extensive scarring and tissue dysfunction when it occurs in postnatal life. Pathological wound healing places a huge burden on society; besides the emotional and physical toll that these processes take on individuals, the economic cost of disease reaches into tens of billions of dollars annually. Recently, evidence emerged to show that adult bone marrow-derived mesenchymal stem cells (BMSCs) traffic to wounds and injured tissues in postnatal life and mediate tissue repair. Subsequently, Dr. Fauza’s laboratory has shown that MSCs derived from amniotic fluid (aMSCs) play a significant role in fetal wound healing. In contrast to wound healing in adults, fetal wound healing is almost scarless, restoring virtually normal form and function to the repaired tissue.

Hypothesis: We hypothesized that aMSCs might be better than bMSCs at promoting wound healing in a post-natal setting. To test this hypothesis, the goal of this project was to compare the impact of aMSCs versus bMSCs in a model of controlled wound healing.

Methods: First, it was necessary to determine and compare the tolerance of aMSCs and bMSCs to hypoxia, as tolerance to hypoxia is a determining factor in the therapeutic applicability of cells. To that end, human bMSCs and aMSCs, duly characterized by flow cytometry, were plated at equal densities and allowed to grow for 7 days in hypoxic (1% O₂) or normoxic (20% O₂) conditions, with the following analyses conducted at days 1, 3, 5, and 7: cell proliferation kinetics were measured by cell count and the BrdU incorporation assay, and western blot for markers of hypoxia tolerance (HIF1a, Sox9, osteocalcin).

Results: Analysis of the results is currently in progress.

Discussion: Properly defining cells’ responses to hypoxia is a virtual pre-requisite to their application therapeutically, hence this step being taken. Surprisingly, such determinations remain to be described in aMSCs, as well as how these cells compare in that regard to bMSCs. The actual application of these cells in a rodent model of wound healing will be our next step.

If successful, this research has the potential to lead to the improvement of wound healing in a clinical setting and to lessen the burden of improper tissue repair on individual patients and on society.
Culturing Astrocytes from Adult Mice: A model for Neuron-Glia Interaction after Injury

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Astrocytes are the most abundant cell type in the central nervous system. Once conceived as ‘neural glue,’ these cells are now known to play numerous essential regulatory and supportive functions in neural biology. Importantly, astrocytes become ‘reactive’ in response to all known neural insults in a process that involves transcriptional changes, cell division and hypertrophy. Reactive astrocytes serve to stabilize the injury site acutely, however, in adult mammals specifically, the cells also form a ‘glial scar’ that permanently prohibits axon growth and synapse formation.

To date, culture methods can only yield astrocytes from the brains of neonatal mice, which are highly supportive of neurons in vitro. The inability to culture adult astrocytes represents a major barrier to understanding the anti-regenerative environment that hinders recovery from neural insults in mature mammals. To address this gap, we aimed to introduce a protocol to culture astrocytes from adult mice, and use it as the foundation of a co-culture system with neurons. We hypothesized that unlike astrocytes cultured from neonatal mice, these cells would be non-supportive for neurons in vitro.

After establishing a basic protocol, we manipulated a number of internal variables, including the age of the mice, pre-harvest interventions, and various aspects of the culture conditions. We also obtained immunostaining and microarray data to verify the purity and yield of the product. These efforts produced the following results: 1) >90% of the cultured cells express the canonical astrocyte markers GFAP, Aquaporin 4, and S100B. 2) Microarray comparison of cultured cells from early postnatal and 21 day-old mice showed differential expression in ≈ 400 genes, including complement and cytokine pathways. 3) A cortical stab injury model increased astrocyte yield fivefold, from 50,000 to 200,000 cells/mouse, without having a significant effect on expression patterns. 4) The capacity of reactive astrocytes to support neuron survival in vitro declines steadily as the age of the animal increases. This effect was observed with mouse ES-cell derived spinal motor neurons and primary cortical interneurons. Current efforts are underway to characterize this neural phenotype in terms of arborization and synapse formation.

These results, while preliminary, affirm the possibility of an astrocyte/neuron co-culture system can recapitulate important aspects of the cellular and molecular environment after neural injury in vivo. We hope that this system will facilitate study of the crucial interactions that occur between neurons and their glial counterparts during pathological insults to the nervous system.
Plasmacytoid Dendritic Cell Induction of Allogenic Regulatory T cells

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Plasmacytoid dendritic cells (pDCs) are antigen presenting cells that have been implicated in promoting immune tolerance, preventing organ allograft rejection, and mounting an anti-viral immune response. Although in-vivo models have illustrated these outcomes, the precise mechanistic pathway by which they induce immune tolerance remains unclear. Life sustaining, full MHC-mismatched mouse kidney transplants are spontaneously accepted and in turn promote systemic tolerance of skin or heart grafts in some strain combinations (e.g., DBA/2J to B6). In order to evaluate their potential role in promoting acceptance during allogeneic transplantation, we isolated pDCs from the bone marrow (BM), spleen, and kidney organs of DBA/2J mice. Using flow cytometry, we examined pDC surface antigens (PDCA-1, B220, CCR-9, CD-103, CD-86, CD-80, DEC-205, and CD123) to assess purity and characterize their level of maturity. We then isolated CD4+CD25- T cells from the spleens of B6 Foxp3eGFP mice. We co-cultured the pDCs and T cells with and without IL-2 and TGF-B cytokines. This mixed lymphocytic reaction was analyzed after 4 days for the increase of CD4+CD25+Foxp3+ regulatory T cells (Tregs), as determined by flow cytometry and using GFP luminescence. In the presence of cytokines, BM pDCs induced 35.7% of naive T cells to become Tregs. Spleen and kidney pDCs elicited induction of 20.5% and 34.3%, respectively. To further explore their immunological contribution, we adapted the experimental assay to study their biological function in response to sonicated cells, FLT-3 ligand, and lipopolysaccharide (LPS). Based on their antigen presenting properties, we exposed pDCs to sonicated spleen and kidney cells for 24 hours before co-culturing them with naive T cells. While BM- and spleen-derived pDCs, exposed to sonicated cells, were inhibited in their ability to convert naive T cells to Tregs, the exposed kidney pDCs evoked an increased induction of Tregs in-vitro, suggesting that kidney pDCs may differ functionally than their counterparts from other organs and may help explain spontaneous renal transplant tolerance observed in certain mouse strain combinations. While FLT-3 exposure yielded no significant changes, LPS treatment demonstrated an increase in CD80/86 antigens, coinciding with a rapid onset of pDC maturation and reduced Treg induction. Overall, these results provide a more detailed foundation for further investigation of the pathway by which pDCs can modulate the immune system to accept an organ transplantation.
Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age. This complex, heterogeneous disorder can cause a variety of phenotypic features, including irregular menses, polycystic morphology, and/or hyperandrogenism. This phenotypic variability has been a persistent challenge to efforts to identify the etiology and pathophysiology of PCOS.

Recent research efforts have utilized genome wide single nucleotide polymorphism (SNP) association analyses to identify potential PCOS risk genes. A previous genome-wide association study in Han Chinese women identified three PCOS susceptibility loci. Our group demonstrated that risk variants, rs10986105-G and rs10818854-A, on 9q33.3 were also associated with PCOS in women of European ancestry. These variants are located in the third intron of the DENND1A gene, which regulates Rab GTPases. Thus, these variants may be involved in the release of gonadotropins, which rely on Rab GTPases for exocytosis. We hypothesized that these variants would be associated with gonadotropins and LH pulse parameters.

To test the hypothesis, the relationship between these risk variants and gonadotropin levels and pulse dynamics were examined. Subjects were a subset of PCOS patients (n=47) whom had undergone frequent blood sampling and genotyping using primer extension of multiplex products with detection by MALDI-TOF mass spectroscopy. LH pulsatile secretion parameters were calculated using the modified Santen and Bardin method. Pulse parameters and hormone levels were log normalized and the relationship between these parameters and genotype was examined using linear regression with an additive genetic model.

Results revealed that there was no difference between mean LH (19.3±2.1 vs. 29.1±12.4 IU/L; TT vs. TG) or FSH (10.3±0.4 vs. 12.1±1.8 IU/L) levels, LH pulse amplitude (7.2±0.8 vs. 8.9±2.6 IU/L; p), or LH pulse frequency (15.5±0.9 vs. 19.4±2.6 pulses/24 hours) in carriers of the common rs10986105-T or the risk G allele (all p>0.05). Similarly, there was no difference between LH (29.1±14.3 vs. 20.5±2.3 IU/L; GG vs. GA) or FSH (10.3±0.4 vs. 12.1±2.6 IU/L) levels, LH pulse amplitude (8.0±2.6 vs. 7.5±0.8 IU/L; p), or LH pulse frequency (19.7±2.6 vs. 15.7±0.9 pulses/24 hours) between carriers of the common rs10818854-G or the risk A allele (all p>0.05).

Thus, DENND1A PCOS risk variants do not appear to be associated with gonadotropin levels or LH pulse parameters. The results are consistent with data from LH levels in the larger group of PCOS subjects examined previously (n=1415). Additional studies are needed to examine the relationship between these PCOS risk variants and the expression of neighboring genes.
Retrospective Review: Clinical Outcomes of Spinal Cord Untethering in Myelomeningocele Patients Prior to Scoliosis Correction

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Patients with myelomeningocele, a severe form of Spina Bifida, are born with their spinal cord exposed and require an immediate surgical closure operation. Later in life, essentially all patients with surgically corrected myelomeningocele develop a tethered spinal cord in which the spinal cord becomes pathologically tethered to vertebrae. Additionally, they are predisposed to developing scoliosis and neurological manifestations such as a neurogenic bladder. For those who develop scoliosis, a spinal fusion operation is often required to straighten and lengthen the vertebral column. Such an operation could theoretically put tension on a tethered spinal cord and exacerbate neurologic symptoms.

Currently, there is not a clear consensus in the field of neurosurgery as to whether untethering of the spinal cord is necessary in patients with myelomeningocele who present for spinal fusion operations to correct their scoliosis.

The purpose of this study is to identify whether spinal cord untethering is necessary in patients with myelomeningocele who present for a spinal fusion operation. This study compares the post-operative outcomes of patients with myelomeningocele who have exclusively undergone a spinal fusion operation to those patients who have had a spinal cord untethering operation prior to or during their spinal fusion operation.

Our objective is to compare multiple post-operative outcomes in the two patient groups and to determine which had the better outcomes at 6 months of follow-up. We retrospectively viewed 128 patient charts, collecting urodynamic data, NEM functional scores, presenting complaints, and post-operative complications. Many of the patients failed to meet our initial inclusion criteria primarily due to incomplete electronic medical records. This resulted in a group of 38 fusion-only patients and 9 combined fusion and untethered patients for which we were able to collect complete data on.

Data analysis is ongoing. A comparison of pre/post-fusion NEM scores between each patient group will be our primary outcome measure. A significant limitation of this study is the availability of patients meeting our inclusion criteria, thereby resulting in a small sample size. In addition, although NEM scores have been used in other studies to assess different aspects of patient function, they are subjective measures that reflect both the physician’s perception of the patient and the researcher’s interpretation of the physician’s written notes.
Neuroinflammation and White Matter Change in TBI: A Potential New Diagnostic and Therapeutic Approach

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Traumatic Brain Injury (TBI) is a major public health problem, affecting over 2 million people each year. TBI is a sudden physical injury to the brain caused by an external force, which often leads to permanent neurological deficits, impaired behavioral functioning, or death. One of the largest challenges with TBI is the unpredictability of patient’s outcomes. In complicated mild TBI (CmTBI), in particular, it is especially difficult to determine which patients will recover versus which will suffer long-term neurological and cognitive sequelae.

Past research suggests that there are secondary neurological events after the initial TBI, which trigger a neuroinflammatory response. Research suggests that neuroinflammation may be important in determining a patient’s outcome. We hypothesized that the pattern of neuroinflammation, as it relates to white matter damage and micro-hemorrhaging, correlates to specific outcomes experienced by patients who sustain a CmTBI.

To examine the role of neuroinflammation, 10 patients suffering a CmTBI will be recruited from BWH’s Emergency Department for testing and imaging at 1-2 weeks following injury, and then 3 months following the initial injury. PET imaging will be performed using a peripheral benzodiazepine receptor ligand, [11C]-PK11195, as a marker of neuroinflammation. PET results will be combined with data from Diffusion Tensor Imaging (DTI), showing diffuse axonal injury, and Susceptibility Weighted Imaging (SWI), showing micro-hemorrhaging. Neuropsychological testing will be performed to identify cognitive/behavioral sequelae corresponding to these imaging results.

Results have yet to be obtained, as scanning will not begin in late September. Past work has involved a literature review of the PK-11195 marker, developing a protocol for recruiting and maintaining patients involvement over the three-month time course, screening criteria, and obtaining proper equipment. Literature reviews were also completed on complicated TBI and neuroinflammation. PET scans were observed to determine the detailed protocol to be used in this study.

One of the main limitations will be obtaining informed consent from neurologically impaired patients. Dr. Martha Shenton will use a Mini Mental Status Exam to determine capacity to consent. Another limitation is the unpredictability of patient recruitment from the ED, which may interfere with planning/staffing for performing tests and imaging.

The observations made in this project might provide valuable insight into the pathological mechanism of developing long-term neurological outcomes in complicated mTBI. Neuroinflammation may prove to be a helpful diagnostic predictor for outcome, and enable improved management of mTBI, such as the appropriate use anti-inflammatory agents.
Performance of novice versus experienced users on a 3D immersive haptic simulator: A pilot study

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This study evaluates the performance of novice versus experienced users on a simulated caries removal exercise using a newly designed haptic simulator. The novice group consisted of 12 first year dental students with no formal preclinical training and the experienced group consisted of 14 members of a Prosthodontics residency program. Both groups received equivalent calibration training on the simulator and repeated the same caries removal exercise three times. Novice and experienced subjects’ average performance differed significantly on the caries removal exercise with respect to the percent carious lesion removed and volume of surrounding sound tooth structure removed ($p<0.05$). Experienced subjects removed a greater portion of the carious lesion and also a greater volume of the surrounding tooth structure. Efficiency, defined as percent carious lesion removed over drilling time, improved significantly over the course of the experiment for both novice and experienced subjects ($p<0.001$). Within the limitations of this pilot study, experienced subjects removed a greater portion of carious lesion on a 3D immersive haptic simulator.
A Qualitative Study of the Pediatric-to-Adult Care Transition in Patients with Type I Diabetes

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The transition from pediatric to adult medical care can involve significant medical, psychosocial, and developmental challenges for chronically ill patients. These issues are especially salient for patients with type I diabetes (T1DM), which requires extensive daily dietary management, insulin injections and glucose monitoring. Each year, 15,000 people are newly diagnosed with T1DM and the prevalence of T1DM is expected to increase over time. Although the need for improved transitional care has been identified within this population, few have employed qualitative methods to examine transition experiences.

Based on previous qualitative research utilizing focus groups and surveys within this population, we hypothesized that patients would identify significant difficulties during the transition period including gaps in care, gaps in health insurance coverage, worsened disease management, difficulties navigating the healthcare system, difficulties adjusting to new providers or care settings, psychosocial issues and other challenges.

The goal of this study was to collect narratives (n = 20) from a purposive sample of T1DM patients (ages 22-30) who are current patients at Joslin Diabetes Center (Boston, MA). Through semi-structured, in-person interviews, we collected detailed retrospective data on patient’s experiences during the transition period. Interviews were conducted in the Boston area by a single member of the research team and recorded using a digital audio recorder. Patients were asked a pre-defined set of open-ended questions related to their experiences with T1DM and their transition from pediatric to adult care.

To date, sixteen of twenty in-person interviews have been completed (75% female, average age: 25.9). Interviews ranged in length from 35 to 57 minutes (mean: 44 min). Once data collection is concluded, all interview tapes will be transcribed. These transcripts will be individually coded for common themes by 3 members of the research team using a grounded theory approach. Readers will meet periodically to compare coding of transcripts and establish consensus on common themes.

Preliminary data indicate that the transitional period presents significant challenges to patients with T1DM and that transition experiences are highly varied across individual patients and care settings. Commonly described themes included gaps in medical care, worsened disease management and psychosocial issues during and following the transition period. One important limitation of this study is that it involves a small sample at a single diabetes care center. As a result, these findings may not be generalizable to larger T1DM populations.
Identifying Sensory-Specific Brain Resting State Networks

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The resting state networks (RSN’s) refer to the collection of brain circuits active while a person is in a neutral, mind-wandering resting state. Numerous individual RSN’s comprise this collection, including one associated with self-reflective cognition (termed the default mode network, or DMN) and others associated with general sensory rest. However, most RSN’s among this collection remain unidentified and poorly understood.

Mindfulness-based meditative practices may lend unique insight into the sensory RSN’s active during rest. Practitioners have the capacity to voluntarily transition between 4 distinct states of rest, each associated with specific sensory modalities. Each form of rest likely recruits discrete neural networks associated with that sensory modality, which combine together and with additional networks (e.g., the DMN) to form the RSN’s that exist across human populations; thus, identifying these independent resting networks may provide clarity and nuance in our understanding of the RSN’s as a whole.

Disentangling the RSN’s may also lend insight into mental illnesses. Schizophrenia is associated with hyperactive RSN’s, but the currently vague characterization of the RSN’s obscures the precise nature and consequence of this dysfunction. Identifying independent, sensory-specific RSN’s may allow us to determine whether schizophrenic RSN dysfunction is more pronounced in particular subsets of RSN’s.

The subjects were 15 healthy expert meditators (with over 10,000 hours of practice) who were instructed to engage in a specific meditation routine while in a blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD fMRI) scanner. The fMRI methodology exploits the magnetic properties of blood to measure oxygen metabolism in the brain, which in turn is considered a proxy for neural activity. The meditation routine included four different sensory-specific resting states – visual, auditory, somatic, and absolute resting states – as well as a traditional resting state. Brain scans during each state were obtained.

The data from these scans are currently under analysis. These analyses will determine the neural networks activated by the sensory-specific resting states, which can be compared to historical resting scans of controls (to determine whether the sensory-specific networks are present among their RSN’s) and schizophrenic patients (to determine whether schizophrenic RSN hyperactivity is disproportionately present in the sensory-specific resting networks). Identifying the sensory components of the resting state network will lead to a better characterization of this ubiquitous brain state, and identifying the circuits dysfunctional in schizophrenia may lead to a better understanding of the illness and potential avenues for treatment research.
Actigraphy-Based Sleep Characteristics as Predictors of Inflammatory, Autonomic, and Stress Systems Activation in Individuals Suffering From Primary Insomnia

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Although insomnia is one of the most prevalent sleep disorders affecting over one-third of the population, there is a lack of congruent information on the biological consequences of this disorder regarding inflammatory, autonomic, and stress (hypothalamic-pituitary-adrenal, HPA) systems activation. This is partly due to the high heterogeneity of the disorder in terms of its sleep characteristics, for example time to fall asleep, time staying awake at night, fragmentation of sleep, or total duration of sleep. This project raises the question to which extent these sleep characteristics can predict activation in the inflammatory, autonomic, and HPA system. This knowledge will help to identify those individuals with insomnia who are at increased risk for the development of a variety of disorders associated with chronic activation of these systems, such as diabetes, cardiovascular disorders, as well as mood- and pain-related disorders.

We examined 32 participants (age 25±1 yrs, 63% women) with a diagnosis of primary insomnia, i.e. participants have to experience difficulties falling asleep, staying asleep, or feeling poorly rested, independent of a medical or psychiatric condition. We also examined a control group of 19 healthy sleepers (age 25±1 yrs, 68% women). An initial screening visit was followed by a 2 week at-home evaluation keeping a sleep diary and wearing an actigraphy to calculate sleep variables. The study concluded with a second visit to the Research Center in which blood pressure was taken along with a fasted blood draw at 11:30am, and the subjects brought in a sample of their overnight urine collection. The actigraphy-based variables sleep duration, sleep latency (SL), wake after sleep onset (WASO), and sleep fragmentation (SF) were averaged across the 2-week-recording period and entered as dependent variables in regression analyses. Composite scores were calculated for the autonomic (blood pressure, norepinephrine), inflammatory (monocyte counts, interleukin-6, C-reactive protein), and HPA systems (cortisol), and used as predictor variables in regression analyses.

Compared to controls, individuals with primary insomnia had on average higher activation in the autonomic system (p=0.16), HPA system (p=0.09), and significantly higher activation in the inflammatory system (p=0.01). Within the insomnia group, no sleep variables predicted activation in the inflammatory or autonomic systems, while WASO was a significant predictor of HPA activation (beta=0.54, p=0.003). This prediction remained significant after controlling for depression/anxiety levels.

These results suggest that individuals with primary insomnia characterized by problems staying asleep may be at increased risk for disorders associated with HPA-system activation, such as depression.
The Readability of Online Consumer Health Information: a Meta-Analysis

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Patients and families increasingly look to the Internet to research information about their health problems or seek answers to their health questions. Estimates show that seeking health information online now represents the third most common use of the Internet among Americans. The fundamental issue lies in the fact that readable content is difficult to find. For a majority (59%) of adults with one or more chronic conditions, the health information they found online was not helpful. Over the past decade, the concept of health literacy has matured and its importance as a correlate to quality health outcomes clearly shown. Readability, though not the sole factor, is a critical component of a patient’s health literacy and an easily measured characteristic of health information online. Many studies have acknowledged the importance of readability and used validated tools to evaluate subsets of health content online. This meta-analysis attempts to be the first large-scale evaluation of the literature, across disciplines, surrounding the readability of online health content.

Six databases were searched (PubMed, Web of Science, Embase, Cinahl, Eric, and PsychInfo) for peer reviewed journal articles on the subject of the readability of online health information. Articles that were duplicates, did not evaluate content in English, did not evaluate health content online, did not use a validated tool for measuring the readability of the content of interest, or failed to meet additional inclusion criteria were excluded. Acceptable, validated readability tools included but were not limited to Flesch-Kincaid and SMOG. These tests evaluate a block of text using unique algorithms that factor in sentence and word length and output a grade-level score. This score implies that a person would need to have a literacy level at the grade-level, or higher, to comprehend the text. Unique software scripts, using the Perl scripting language on a UNIX platform, were written to iterate over the raw database records and identify the records that would be included or excluded based on novel text evaluating algorithms. These algorithms excluded all but 142 relevant articles.

Evaluation of the individual journal articles, their data and analyses, is currently still in progress. Preliminary evaluations appear to indicate that over the past ten years or more, online health content has been presented at a readability level far above the ability of the average American patient.
Smiles 4 Life

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According to a 2007 Centers for Disease Control and Prevention (CDC) study, oral health status for Americans has progressively improved over the past decade; however, incidence of caries actually increased 15 percent for children between 2 and 5 years old. Dental caries remain the most common childhood disease, being five times more common than asthma and seven times more common than hay fever. The CDC survey also found that dental decay disproportionally affects children living below the federal poverty level. In fact, the likelihood of poor kids ages 2 to 11 to have untreated decay is two times more than their affluent peers. According to the most recent National Health and Nutrition Examination Survey, Mexican American children and non Hispanic black children fare worse than white children in dental health, having over 12% and 15% more untreated decay respectively. The consequences of poor oral health among children are alarming and long lasting, as they greatly impact children’s permanent teeth development as well as overall health. However, with the appropriate prevention measures such as brushing with fluoride toothpaste, dental sealants and regular cleanings, dental caries can be completely preventable.

The Smiles 4 Life community service project was established to advance the oral health status of high-need children in the greater Boston area by providing oral health education, activities, and resources through energetic, interactive lessons. In 2012, Smiles 4 Life continued this mission by targeting education sessions at local community centers with after school programs such as the Vine Street Community Center in Jamaica Plain. These education sessions instructed children in grades kindergarten up through fourth grade on the following: the role that the mouth and teeth play in everyday life, the importance of choosing healthy and nutritious foods and drinks when eating and snacking, how to use proper brushing & flossing techniques to clean teeth and gums, and the role of the dentist in maintenance of good oral care and why it is important for everyone to see the dentist. As a reward for their participation and attention, students received an oral health tool kit. This kit is the foundation for future success with oral health and includes: a child themed toothbrush, toothpaste, a two-minute brushing timer, and a pamphlet of oral health reminders & games. The long-term goal is to ensure that the skills we teach live on with the child after they leave the education session.
The Role of Physiological Neuronal Activity in Postnatal Gliogenesis

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In humans, maturation of the neural circuits required for high-level cognitive and motor functions occurs throughout childhood, adolescence, and young adulthood. The generation of mature oligodendroglial and astroglial cells, which contribute to synapse formation, neuronal support, and myelin sheath development, is critical for the proper function of these neural circuits. While it has been well established that the brain does not complete myelination until the end of the third decade of life, to date our understanding of the precise spatiotemporal pattern of postnatal neural circuit myelination and the mechanisms underlying these processes remains limited. Furthermore, white matter maldevelopment has been implicated in a range of neurological and psychiatric diseases, including cerebral palsy and the cognitive dysfunction that results from cancer therapy. The lack of effective treatment options for these diseases highlights the need to better understand the physiological processes underlying white matter development and regeneration in the postnatal brain.

Previously, we identified a novel early glial precursor cell type in the postnatal human brainstem that appears to contribute to a discrete wave of oligodendroglialogenesis related to corticospinal tract myelination during middle childhood. Here, we use the correlate precursor cell population in mice to probe the hypothesized role of physiological neuronal electrical activity in defining the gliogenic microenvironment that drives oligodendrocyte precursor cell (OPC) proliferation and differentiation. We applied unilateral optogenetic stimulation to the motor cortex of Thy1-channelrhodopsin (Thy1-ChR2) mice for one week beginning at postnatal day (P) 28 and then evaluated the effect on cell proliferation four weeks later. Stereological analysis of EdU-labeled cells revealed robust cell proliferation in response to optogenetic stimulation, with 1,749 +/- 475 EdU+ cells in the stimulated side of the motor cortex versus 300 +/- 102 cells in the non-stimulated (internal control) side. The majority (68 +/- 1%) of these dividing cells expressed the oligodendroglial lineage marker Olig2, indicating OPC or early oligodendrocyte identity. Furthermore, to control for the effects of fiber placement, light, and heat, P28 wild-type control animals (no opsin present) were identically stimulated. No difference in cell proliferation was observed between the stimulated and unstimulated sides of the motor cortex in wild-type animals. These preliminary results indicate brisk OPC recruitment and proliferation in response to physiological neuronal activity in the postnatal brain of the juvenile mouse. Further investigation into the underlying mechanisms may provide powerful insight into potential therapeutic targets in a range of pediatric and adult white matter diseases.
Attitudes and Perceptions of Residents Regarding the Decision-Making Process in a Peripheral Hospital of Mumbai

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Unique cultural, religious, social, and historical forces shape conceptions of individuality and community in India. These conceptions, furthermore, affect understanding and application of human values and the content of morality and ethics. As such, traditional bioethical concepts as constructed in the West and reinforced in much recent medical literature—such as the primacy of patient autonomy and informed consent—do not necessarily or automatically resonate in the Indian context.

Previous research indicates that patients in India often do not make autonomous healthcare decisions. Family constraints, physician advice, and gender inequality have been identified as a few of the factors that contribute to diminished patient autonomy in India. To date, there is limited understanding of the contributory role of resident doctors in the decision-making process of patients. Understanding the perspectives of residents is important because they deliver much of the medical care in major hospitals, especially in metropolitan cities across India. As such, the perceptions about autonomy and informed consent and the actions of resident doctors to implement these ethical safeguards may directly impact the ability of individual patients to make informed, autonomous decisions.

We hypothesized that resident doctors in India have beliefs and perspectives about patient autonomy that are distinct from what is taught in medical schools in the US. In order to understand the attitudes of resident doctors regarding the factors that affect patient autonomy and to identify residents’ beliefs about the decisions that patients make, 14 residents from various departments at K.B. Bhabha Hospital were interviewed. Residents were selected based on their willingness to participate in the study and were excluded if they chose to not consent to the terms of the study. The semi-guided interviews focused on several areas, including residents’ motivations for choosing medical careers, residents’ understanding of bioethical concepts, and residents’ understanding of normative concepts.

The analysis of the interviews will explore the following domains: the educational background of the residents and the impact that their training may have on their understanding of autonomy; how, according to the residents, patients make decisions, and the factors that affect the decisions patients make, including culture, family, and gender; and the attitudes of residents toward the decisions that individuals make. Analysis of the data may yield new hypotheses regarding the transmissibility of normative beliefs across culturally distinct societies.
Evaluating the Function of Young and Old Thymus Grafts Using sjTREC Analysis and Cortex/Medullary Ratios After Transplant Into Young or Old Miniature Swine Recipients

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Recently thymus transplantation has emerged as a promising approach for tolerance induction in organ transplantation. In miniature swine, vascularized thymus grafts successfully induce tolerance to renal and cardiac grafts despite class I or full MHC mismatches. In later studies, involuted thymus transplanted into young recipients become rejuvenated and regained the ability to induce tolerance to allogeneic renal grafts. These findings point to thymus transplantation as a means to obtain tolerance in organ transplant recipients if involuted thymus tissue can be successfully and reproducibly rejuvenated.

To better understand the process of thymic rejuvenation in miniature swine, this study seeks to determine the relative importance of young bone marrow and the young microenvironment of a juvenile swine during the rejuvenation of involuted thymus grafts. Thymus grafts were transplanted into either young or old recipients that received syngeneic bone marrow transplants (BMT) from either young or old donors. Recipients were first thymectomized, and two weeks later, received a syngeneic BMT. Three weeks after BMT, allogeneic vascularized thymic grafts were transplanted into the recipients which were then treated with a 12-day course of FK506. At day zero and months two, four, and six post-transplant, graft biopsies were obtained, cortex-medullary ratios were determined histologically, and quantification of signal-joint T Cell Receptor Excision Circle (sjTREC) content was performed using polymerase chain reaction to determine the rejuvenated status of the transplanted thymus.

The experiment is currently ongoing and results of this assay are still being analyzed. Thymus biopsies from one animal has been completely analyzed according to protocol, and there are 11 more animals whose samples have not been completely analyzed or obtained given the longitudinal nature of this study. As expected, aged bone marrow and the microenvironment of an old swine causes the sjTREC content to decrease and the cortex-medullary ratio to decrease more quickly in a transplanted young thymic graft relative to a native thymus in a young swine, indicating a quicker involution. Before any firm conclusions can be made, however, the remaining animals need to be completely analyzed to determine the relative importance of the bone marrow and microenvironment of the recipient swine during thymic rejuvenation.
Identifying Dental Panoramic Radiograph Features for the Screening of Osteoporosis in Post-Menopausal Women

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Osteoporosis is characterized as loss of bone mineral density and deterioration of bone architecture, with consequent susceptibility to fractures, even with minimal force. Osteoporosis is defined by the World Health Organization as a bone mineral density (BMD) that is -2.5 standard deviations below the mean as measured by DEXA. Early detection of osteoporosis is an important public health goal because interventions such as drug therapy, exercise, and fall-preventing measures can be effective in preventing fractures. The acceleration of bone degeneration during menopause causes post-menopausal women to be especially prone to complications arising from osteoporosis.

Dental panoramic radiographs are a routine part of dental care that are often used in check-ups and treatment planning. Dental radiographs have great potential as a screening tool for osteoporosis because of their wide availability, practicality, and low cost.

To test if dental panoramic radiographs are useful in screening for osteoporosis we are conducting a retrospective cohort study to compare measurements taken from radiographs with bone mineral density measurements obtained by DEXA. Our study population consists of women over the age of 50 who have been a patient at the Massachusetts General Hospital Department of Oral Surgery and have had a dental panoramic radiograph, DEXA measurement, and chest x-ray (n=278). The panoramic measurements of interest are the gonial and antegonial angles. In addition, demographic information and other oral health measurements including number of teeth, periodontal status, and cortical bone outline will also be collected. Diagnosis of osteoporosis by chest x-ray will serve as a secondary outcome to compare the usefulness of panoramic radiography in screening for osteoporosis. Linear regression analysis will be used to analyze the relationship between panoramic markers and BMD. In addition, an ROC curve will be used to determine sensitivity, specificity, and determine threshold values for BMD testing referral. Currently, we are finishing collecting demographic data and will soon statistically analyze the data.
Efficiency and Accuracy of Digital vs. Conventional Impressions for Implant Rehabilitations

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With current CAD/CAM techniques, digital technologies once limited to the scanning and milling of tooth-supported fixed prostheses can now support the implant impression process. However, there are few published studies on the performance of the digital impression in implant restorations. A digital impression system for implant restorations would be beneficial to patients and dental practitioners in several ways: 1) elimination of the uncomfortable experience of making a conventional impression, 2) elimination of variables in the conventional technique that can lead to inaccuracies in the final restoration or stress the integrity of the implant, 3) visualization of the preparation three-dimensionally, and 4) potential cost- and time-effectiveness.

Thirty HSDM 2nd-year dental students performed digital and conventional impressions of the control Typodont with a single implant on maxillary right first premolar. Inclusion criteria were that the participants were in their second year at HSDM and had no prior experience with impression taking.

For the conventional technique, thirty closed tray fixture level impressions of the typodont were made using polyvinyl siloxane with a stock tray material. The obtained control impressions were poured after attaching the analogue on #5 in Type III dental stone within 30 minutes.

For the digital impression technique, thirty impressions of the quadrant were made using i-Tero scanner. The electronic data were sent to an iTero-certified dental laboratory. Models were milled out of polyurethane blocks to make master digital models.

The efficiency and accuracy of each technique was analyzed. To study efficiency, the amount of time taken for each impression technique was measured in three categories: preparation time, working time, and retaking time. To study accuracy, the 30 stone models from the conventional impression and the 30 milled models from the digital impression were compared to the control typodont. A CAD/CAM scanner was used to scan all 60 models and the control model. The resultant three-dimensional virtual model data were analyzed using Geomagic Qualify software. The discrepancies of dimensions were calculated as the deviation in measurement in comparison to the original Typodont model.

Mean total treatment time was 24:42 m/s for conventional and 12:29 m/s for digital impressions (p<0.001). Mean preparation time was 4:42 m/s for conventional and 3:35 m/s for digital impressions (p<0.001). Mean working time was 20:00 m/s for conventional and 8:54 m/s for digital impressions (p<0.001). These results indicate that the digital technique is more efficient than the conventional technique. Data on accuracy are currently being analyzed.
Large-Scale Synthesis of a 2-Aminoimidazole/Triazole Derivative Capable of Suppressing Oxacillin Resistance in MRSA

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The rapidly increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in both the community and hospital settings represents a major challenge in medicine today. As resistance to nearly all β-lactam antibiotics has been acquired, doctors are left with few choices on how to treat these infections. Research has shown that small molecules can be used as adjuvants that resensitize drug-resistant bacteria to traditional antibiotic therapy. Recently, a 2-aminoimidazole/triazole (2-AIT) derivative has been shown to resensitize MRSA to the effects of oxacillin. Due to the need for *in vivo* testing of this compound, a large quantity of this compound was required. The goal of this project was to synthesize approximately five grams of the lead compound, as well as to screen the compound’s ability to lower oxacillin resistance in MRSA.

The large-scale synthesis was accomplished via reductive amination of an α-amino ethyl ester/alkyne with the commercially available 4-butylbenzaldehyde. Following BOC-protection, the α-amino ethyl ester/alkyne was reacted with a previously synthesized azide under Huisgen cycloaddition conditions. This was converted to the Weinreb amide, which was reduced and deprotected. Cyclization with cyanamide then yielded the desired amount of the 2-aminoimidazole/triazole conjugate.

Using a microdilution protocol in 96-well microplates, the minimum inhibitory concentration against MRSA was determined for oxacillin alone and oxacillin in the presence of the 2-AIT conjugate. Initial assays have shown that this compound is capable of suppressing oxacillin resistance in MRSA isolates by up to 128-fold *in vitro*, allowing traditional antibiotic therapy to remain effective. Further research will use the compound synthesized in this project to evaluate its effects *in vivo*. 
Characterizing Cell-Specific Radiation Sensitization Induced by HDAC Inhibition

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Radiation therapy is commonly employed in the treatment of brain, breast, and prostate tumors. γ-irradiation induces cell death through the formation of DNA double strand breaks (DSBs), which halt the cell cycle until the DNA damage is repaired. Despite the targeted nature of radiation therapy, techniques designed to deliver lethal doses to the tumor inevitably expose healthy tissue to an attenuated but significant radiation dose; these affected non-cancerous cells depend on several DNA repair pathways to repair the DSBs generated by radiation therapy.

We are interested in studying potential drugs that have the ability to make tumors more sensitive to radiation, and to protect normal tissue from radiation damage. To this end we examined histone deacetylase (HDAC) inhibitors, small molecules that modify the structural features of chromatin involved in the packaging of DNA. HDAC inhibitors are considered to be potential drug candidates to complement radiation therapy, yet the mechanisms underlying their effects have been elusive.

We hypothesized that HDAC inhibitors act as radiosensitizing agents through one or more of the following mechanisms: augmenting DSB formation, disrupting DSB repair, or altering DNA damage-induced signaling. To study this, we first developed a high-throughput automated microscopy assay to assess effects on elements of DNA damage-mediated signaling through quantification of H2AX phosphorylation, cell cycle profiling, and cell survival following IR-induced DSBs. We then applied this assay to a library of diverse HDAC inhibitors as well as a collection of shRNAs targeting the individual HDACs. We next assessed DSB induction and repair kinetics on a selection of active HDAC inhibitors with CometChip, a novel high-throughput adaptation of the single-cell DSB comet assay developed with collaborators in the laboratory of Bevin Engelward.

Our data suggest that class I HDAC inhibitors potently elevate H2AX phosphorylation, but without strong effects on DSB induction or repair kinetics. Using both FACS analysis and live cell imaging, we find that some HDAC inhibitors also enhance G2/M cell cycle arrest and decreased survival, even in the absence of irradiation. These data suggest that HDAC inhibitors influence radiation effects primarily through altering IR-induced signaling events. This may have important implications for the clinical use of these agents.
Understanding Malnutrition and Diarrhea in Children under 2 at Mayapuri

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Persistent diarrhea and malnutrition constitute the second most prevalent cause of under age 5 mortality in the developing world. Previous studies have shown that certain factors can lead to an increased risk for diarrhea and malnutrition, including the absence of breastfeeding, lack of access to clean water, to environments with clean sanitation, and to the steady availability of healthy foods, all of which are characteristic of slum life. It is imperative to determine the prevalence of diarrhea and malnutrition in Mayapuri, a New Delhi slum, and to find the factors leading to these diseases in order to implement strategies to prevent diarrhea and malnutrition in the first place. We aimed to determine the prevalence of both diarrhea and malnutrition in children under 2 years of age, to assess the access to clean water in the slum, and to see whether there is any correlation between breastfeeding and decreased susceptibility to diarrhea and malnutrition in Mayapuri.

This study used a questionnaire survey to determine which social, cultural, and economic factors are associated with persistent diarrhea and malnutrition. Researchers went from home to home asking parents or older siblings over 16 years of age if they have children or siblings under the age of 2, and if so, if they are willing and available to answer a few questions about their children/siblings.

Of the 200 families with children under age 2, 82 families were surveyed, which corresponded to 98 children. Of the 98 children included, 36% had persistent diarrhea within the last two months, and 23% were classified as being malnourished based on mid-upper arm circumference. Of the children who had persistent diarrhea, 72% had not been breastfed, and of the children who presented with malnutrition, 34% had not been breastfed. Lack of access to clean water was associated with both malnutrition (p<0.02) and diarrhea (p<.04). However, children having access to fresh vegetables was not significant in having diarrhea and malnutrition.

We concluded that breast-feeding correlates with decreased levels of malnutrition and diarrhea; however, ongoing studies must be performed to eliminate confounding and to increase the power of our study. In addition, we learned that access to clean water is essential for children, with boiling water before giving it to children being the most significant avenue to obtain such clean water.
Apathy is Associated with Atrophy of the Inferior Temporal Cortex in Amnestic-Mild Cognitive Impairment and Clinically Normal Individuals

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Recent trials for experimental Alzheimer’s disease (AD) treatments at the stage of mild-moderate dementia have failed to demonstrate clinical efficacy. These negative results may be explained by late therapeutic intervention in the disease’s already advanced pathology. For successful clinical trials, superior biomarker profiles of the earliest stages in AD may be needed for earlier diagnosis and intervention.

Apathy, characterized by social withdrawal and loss of goal oriented behavior, is the neuropsychiatric symptom most commonly associated with AD dementia and one of the most commonly associated with amnestic mild cognitive impairment (MCI), a prodromal stage of dementia. Apathy has been shown to correlate with many regionally specific cortical changes in AD, including atrophy of the medial frontal cortex. Given apathy’s prevalence in MCI, we hypothesized that the medial frontal atrophy associated with apathy in AD dementia may begin during MCI or even earlier in the disease process. If true, such apathy-associated atrophy may be a useful biomarker for clinical trials involving the earliest stages of AD.

To test our hypothesis, we recruited 47 individuals with MCI and 19 clinically normal elderly (CN) individuals. Apathy was assessed using the Apathy Evaluation Scale. Cortical thickness of four regions of interest (ROI)—the bilateral anterior cingulate cortex, inferior temporal cortex, orbitofrontal cortex, and supramarginal cortex, chosen a priori—were assessed with volumetric magnetic resonance imaging (MRI) and FreeSurfer software. To test for a relationship between apathy and cortical thickness, a linear regression model with backward elimination was employed using apathy score as the dependent variable; predictors included cortical thickness of each ROI and the following covariates: diagnosis, age, American National Adult Reading Test IQ (a proxy of premorbid intelligence), Digit Symbol Score (a test of processing speed), and the Rey Auditory Verbal Learning Test total learning score (a test of memory).

Our model suggested a significant association between greater apathy and decreased thickness (or atrophy) of the inferior temporal cortex (p<0.005) and increased thickness of the anterior cingulate cortex (p<0.05) across all subjects. Looking at MCI subjects alone and at CN subjects alone, there was also a significant association between decreased inferior temporal thickness and apathy (p<0.05).

These results suggest that inferior temporal atrophy may be associated with increased apathy in the earliest stages of AD preceding dementia, in contrast to anterior cingulate atrophy that has been associated with apathy at the stage of dementia.
Fertility and family planning on Idjwi Island, DRC: A cross-sectional study

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Idjwi, an island of approximately 220,000 people, is located in eastern DRC and functions semi-autonomously under the governance of two kings (mwamis). At more than 6 live births per woman, Idjwi has one of the highest total fertility rates (TFRs) in the world. Rapid population growth has lead to widespread environmental degradation and food insecurity. Meanwhile family planning services are largely unavailable.

At the invitation of local leaders, we sought to understand Idjwi’s fertility environment. We conducted a representative survey of 2,078 households in 50 enumeration areas in accordance with Measure DHS protocols, and interviewed woman about sexual- and gender-based violence and access to health services. We also interviewed local leaders and health care professionals about the health system. The household survey measured women’s unmet need for contraception, desired number of children, and desire to use contraceptives, among other health outcomes. Using a model of proximate determinates of fertility, we predicted how the introduction of contraceptives and/or extended periods of breastfeeding could reduce the TFR. The main limitation of our research is that the household survey was restricted to women age 18-50 and therefore excludes some young mothers.

Interviews revealed that Idjwi’s extremely high fertility is associated with a weak health care system, poor funding, deteriorating infrastructure, and discrimination and violence against women. In the survey, over half of all women reported an unmet need for spacing or limiting births, and nearly 70% of women named a specific modern method of contraception they would prefer to use; pills (25.4) and injectibles (26.5) were most desired. Based on women’s fertility behaviors and desires, we predicted that an increase in contraceptive prevalence (from 1% to 20%) or an increase in the length of breastfeeding (from 10 to 14 months) could reduce TFR on Idjwi to 5 children per woman, and reduce unmet need for contraception by up to 11%.

To improve the status of women and curb unsustainable population growth, we recommend adding family planning services at health centers with NGO support, reaching out to women during regular medical and maternal health visits, pursuing a community health worker program, promoting extended periods of breastfeeding, and implementing comprehensive community-based programs to end sexual- and gender-based violence toward women. Lessons from Idjwi may be applied to other densely populated, low-income settings with high fertility.
Retrospective Review: Clinical Outcomes of Spinal Cord Untethering in Myelomeningocele Patients Prior to Scoliosis Correction

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Patients with myelomeningocele, a severe form of Spina Bifida, are born with their spinal cord exposed and require an immediate surgical closure operation. Later in life, essentially all patients with surgically corrected myelomeningocele develop a tethered spinal cord in which the spinal cord becomes pathologically tethered to vertebrae. Additionally, they are predisposed to developing scoliosis and neurological manifestations such as a neurogenic bladder. For those who develop scoliosis, a spinal fusion operation is often required to straighten and lengthen the vertebral column. Such an operation could theoretically put tension on a tethered spinal cord and exacerbate neurologic symptoms.

Currently, there is not a clear consensus in the field of neurosurgery as to whether untethering of the spinal cord is necessary in patients with myelomeningocele who present for spinal fusion operations to correct their scoliosis.

The purpose of this study is to identify whether spinal cord untethering is necessary in patients with myelomeningocele who present for a spinal fusion operation. This study compares the post-operative outcomes of patients with myelomeningocele who have exclusively undergone a spinal fusion operation to those patients who have had a spinal cord untethering operation prior to or during their spinal fusion operation.

Our objective is to compare multiple post-operative outcomes in the two patient groups and to determine which had the better outcomes at 6 months of follow-up. We retrospectively viewed 128 patient charts, collecting urodynamic data, NEM functional scores, presenting complaints, and post-operative complications. Many of the patients failed to meet our initial inclusion criteria primarily due to incomplete electronic medical records. This resulted in a group of 38 fusion-only patients and 9 combined fusion and untethered patients for which we were able to collect complete data on.

Data analysis is ongoing. A comparison of pre/post-fusion NEM scores between each patient group will be our primary outcome measure. A significant limitation of this study is the availability of patients meeting our inclusion criteria, thereby resulting in a small sample size. In addition, although NEM scores have been used in other studies to assess different aspects of patient function, they are subjective measures that reflect both the physician’s perception of the patient and the researcher’s interpretation of the physician’s written notes.
Perceptions of Tanzanian Health Care Workers Towards the Use of Mobile Phone Clinical Applications

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The use of mobile phones in health care offers the promise of improved quality of care in developing countries. Despite the promise of this technology in improving health, there is limited literature showing health workers’ perceptions of barriers to mobile phone based applications in a Tanzanian context. Examining the perceptions of these health care workers is vital, as they will provide clear indications for how to ensure maximal adoption of this technology.

Aims of this project were to identify the factors that encourage and discourage use of mobile phone based technology and to explore strategies which address how this technology could be sustainably implemented in health care settings in Tanzania.

Thirty-one semi-structured, in-depth interviews of nurses, community health workers, and their supervisors involved in mobile phone clinical application studies were conducted at sites including seven health centers in the Dar Es Salaam and Pwani regions of Tanzania. Interviewees were selected via purposive sampling based on advice from D-Tree International employees involved in previous studies.

The resulting 20+ hours of recorded interviews are currently being transcribed and translated from Swahili to English. Upon completion, we will analyze these transcripts to identify common themes. A manuscript outlining the findings will be produced for submission to a peer reviewed journal.

A report documenting initial impressions and making recommendations for sustainable implementation of this technology based on the interviews conducted has been prepared and submitted to D-Tree International for distribution to D-tree International staff. This report noted that the Tanzanian health care workers interviewed, and particularly community health workers, viewed use of mobile phones in medical care in a positive light. Some of the challenges to mobile phone use raised by facility-based health care workers led to recommendations in the report including that health care workers be provided with greater, prompter feedback on their performance given the enhanced data collection made possible with mobile phones, that they be made aware of the variety of clinical applications available and the locations of their current use, that security issues surrounding phone usage be given greater consideration, and that responsibility for lost or stolen phones be explicitly communicated.

Limitations of this project include potential for selection bias in interviewee selection, social desirability bias whereby participants may not feel comfortable speaking frankly about disincentives to adoption of this technology, and questionable generalizability of the findings outside of the settings and regions in which interviews were conducted.
Impact of Vaccines on the Reduction of Child Mortality in Developing Countries

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Millennium Development Goal (MDG) 4 targets to reduce the under-5 child mortality rate by two-thirds from 1990 to 2015. Significant progress has led to a 35% reduction in under-five mortality rate; the global under-five mortality rate dropped from 88 deaths per 1,000 live births in 1990 to 57 deaths per 1,000 in 2010. However, a significant portion of which are attributable to vaccine-preventable deaths.

We hypothesized that most child deaths are occurring in the 72 GAVI-eligible countries and that GAVI-eligible countries have the highest rates of child mortality due to the fact that they are the 72 poorest countries in the world with a GNI under $1,520 USD. To determine this, we looked into the latest 2010 data from the World Bank and World Health Organization. Furthermore, for each of the 72 countries, measles vaccine coverage rate, DTP vaccine coverage rate, socioeconomic inequities, and progress of MDG-4 was also assessed.

Vaccine preventable deaths accounted for 17% of all under-five deaths in 2008. Of these deaths, 30% were attributable to the rotavirus, 32% pneumococcal, 13% Hib, 14% pertussis, 8% measles, 4% tetanus.

It is estimated that 90% coverage of vaccines including DPT, Hib, pneumococcal, rotavirus and measles in GAVI-eligible countries, up to 2.5 million under-five deaths could be averted.
A low-cost text message system for community-based maternal and newborn care in rural Nepal

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Every year, nearly 60 million births occur in the absence of a skilled birth attendant, significantly increasing the risk of maternal and neonatal mortality from preventable or easily treatable causes. In rural Nepal, more than 90% of women give birth without a skilled birth attendant and neonatal and maternal mortality are among the worst in the world. Community-based maternal and newborn care (CB-MNC) programs may improve childbirth care for the rural poor, encourage facility births and increase health equity for millions of vulnerable women and children. Nepal has a well-established CB-MNC program that relies on female community health volunteers (FCHVs) to provide basic services and referrals. Rural areas face human resource challenges that make supervision of the FCHV program difficult. We propose a novel mHealth system using text-message (SMS) and SIM application tools on cheap, locally available phones that communicate with a shared database accessible to supervisors on and offline. This system also offers automated reminders and alerts messaging to FCHVs and local health workers to support prenatal, delivery and postnatal care.

Field testing and informal community discussions in potential pilot areas is underway, and the initial results suggest that FCHVs will find a reminders and alerts system meaningful but care must be taken to avoid over-reliance on text-based data collection as most FCHVs are illiterate and unfamiliar with SMS messaging. We aim to incorporate FCHV feedback into a final design in November 2012. In January 2013, we will begin a pilot cluster-randomized controlled trial to assess the impact of an SMS-supported CB-MNC program against a standard CB-MNC program in Baglung District of rural Nepal. We hypothesize this SMS system will improve CB-MNC in rural Nepal by increasing the number of women and newborns receiving appropriate care and referrals. Our primary endpoint is the percentage of women who deliver with a trained provider, determined from paper reports and validated by survey sampling of recently delivered women. We expect this study will demonstrate the feasibility of appropriate technology interventions in resource-limited settings like rural Nepal as well as provide insight into the efficacy of SMS-based communications for quality improvement in maternal and newborn care.
Preoperative 3-Tesla Multiparametric Endorectal MRI Findings and the Odds of Upgrading and Upstaging at Radical Prostatectomy in Men with Clinically Localized Prostate Cancer

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Purpose/Objective(s): Whether 3T multiparametric endorectal MRI (erMRI) can add information to established predictors regarding occult extraprostatic or high-grade prostate cancer (PC) in men with clinically localized PC is unknown.

Materials/Methods: At a single academic center, 118 men with clinically localized PC who underwent radical prostatectomy (RP) between 2008 and 2011 and had a preoperative 3T multiparametric erMRI comprised the study cohort. We performed multivariable logistic regression analyses in all men and the 100 with favorable-risk PC to analyze whether erMRI evidence of T3 disease was associated with prostatectomy T3 or Gleason score (GS) 8-10 (in patients with biopsy GS < 7) PC, adjusting for age, PSA level, clinical T-category, biopsy GS, and percent positive biopsies.

Results: The accuracy of erMRI for extracapsular extension and seminal vesicle invasion was 75% and 95%, respectively. For all men, erMRI evidence of a T3 lesion vs. T2 was associated with increased odds of pT3 disease (adjusted odds ratio (AOR) 4.81, 95% confidence interval (CI) (1.36, 16.98), p=0.015) and pGS 8-10 (AOR 5.56, CI (1.10, 28.18), p=0.038). In men with favorable-risk disease, these results were AOR 4.14, CI (1.03, 16.56), p=0.045 and AOR 7.71, CI (1.36, 43.62), p=0.021, respectively.

Conclusion: 3T multiparametric erMRI in men with favorable-risk PC provides information beyond that contained in known preoperative predictors about the presence of occult extraprostatic and/or high-grade PC which can be used to counsel men who plan to undergo RP or radiotherapy (RT) about the possible need for adjuvant RT or the clinical utility of adding hormone therapy, respectively.
An imaging-based measure of myocardial microstructure to characterize ventricular progression from hypertension to heart failure

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Heart failure (HF) is a leading cause of morbidity and mortality, and is projected to increase in prevalence with population aging. Hypertension is the most common risk factor for HF. Although the progression from hypertension to HF is known to involve changes in left ventricular (LV) structure and function, the pathogenesis remains unclear. Imaging based techniques specifically designed to characterize changes in LV microstructure could be used to detect early myocardial remodeling, serve as measures of the LV response to interventions in experimental studies, and aid in screening for individuals at risk for eventually developing clinical HF.

The goal of this project is to develop and validate a novel imaging based measure of myocardial microstructure that may be used in further investigations of hypertension and HF. We hypothesize that chronic exposure to afterload stress leads to cellular and extracellular alterations of LV myocardium that are reflected in increased myocardial density, as measured by sonographic signal intensity distributions.

A computational method of analysis was developed using ImageJ software to perform measurements of signal intensity distributions. This image analysis method was designed and standardized to (1) minimize inter- and intra-user variability, (2) minimize inter- and intra-subject variability, and (3) identify differences in myocardial density between healthy myocardium and myocardium exposed to afterload stress. Initial validation was performed using a cohort of 12 identical mice studied over a 7 week period: 4 controls, 4 that underwent aortic banding, and 4 that underwent aortic banding and had banding removed at 3 weeks. The image analysis method was applied by a blinded investigator to LV long- and short-axis views of murine echocardiograms that were obtained at regular intervals over the study duration.

Upon completion of the initial validation study, the analysis technique will be applied to clinical echocardiographic images collected from humans with and without hypertension or aortic stenosis. Ability of the method to differentiate between different disease conditions will be evaluated. Because the method is being developed using controlled murine echocardiograms, the extent to which the method may be translated to clinical studies may be impacted by several factors including: variable image quality, technical differences in human and mouse sonographic imaging, and variation in myocardial microstructure across subtypes of afterload-related LV disease in humans. However, if successful, translation of the method from the experimental to the clinical models may provide a valuable tool for gaining greater insight into disease progression from hypertension to HF.
An Automated Electronic Surveillance System for Catheter-associated Urinary Tract Infections in the Intensive Care Unit

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Catheter-associated urinary tract infections (CA-UTIs) account for up to 40% of hospital-acquired infections in United States hospitals each year. The Centers for Medicare and Medicaid Services (CMS) now mandate CA-UTI reporting from all intensive care units (ICUs) to the National Healthcare Safety Network (NHSN). Traditional methods of CA-UTI surveillance based on manual chart review are time- and labor-intensive and prone to error.

The first aim of this study is to develop an electronic surveillance tool based on the NHSN case definition to aid in CA-UTI identification (“electronic algorithm”). The second aim is to compare the sensitivity and specificity of traditional hospital-based surveillance methods (manual chart review) with this electronic algorithm for surveillance of CA-UTIs.

The study is being conducted in a 947-bed teaching hospital. The study population includes all adult patients aged ≥18 years admitted to an ICU from January 1 to June 31, 2012 who were noted to have an indwelling urinary catheter in place at any time during admission. We will identify hospital-acquired CA-UTI using three methods: manual chart review by trained Infection Control Practitioners (traditional surveillance), electronic algorithm alone, and electronic algorithm supplemented by manual chart review (surrogate gold standard). We will calculate the sensitivity, specificity, predictive values, and the kappa statistic between the electronic algorithm-supported chart review and the other methods.

This study is currently ongoing. The manual review of patient charts is complete, with 101 cases identified. We are currently performing validation and revision of the electronic algorithm. When validation is complete, we will compare the cases identified by manual review with the cases identified by the electronic algorithm. All discordant cases will be re-reviewed by two study investigators. This re-review will serve as the surrogate gold standard that we will use for calculation of the sensitivity and specificity of manual review alone and electronic algorithm alone.

This study has several potential limitations. First, no true “gold standard” exists for CA-UTI case identification. As such, we are using cases identified by the electronic algorithm supplemented by chart review as a surrogate gold standard comparator for determination of the sensitivity and specificity of the manual review and electronic algorithm. In addition, although the NHSN CA-UTI case definition includes UTI signs and symptoms (e.g., fever, suprapubic tenderness), the electronic algorithm cannot query this information as it is not collected in the clinical data repository.
The role of CD39 in the modulation of effector/regulatory cell balance in inflammatory bowel disease

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Inflammatory bowel disease (IBD) is associated with excessive inflammation in the bowel and extra intestinal tissues in genetically susceptible individuals. IBD can manifest in two major forms, ulcerative colitis and Crohn’s disease. In IBD, the dynamic balance of regulatory T cells (Treg) to T helper type 17 (Th17) cells in the gut, alterations in bacterial flora, and other environmental factors may modulate local and systemic inflammatory responses.

CD39 is an ectonucleotidase hydrolyzing ATP and ADP into AMP that is subsequently converted into adenosine by CD73, an ectoenzyme working in tandem with CD39. Extracellular adenosine has been implicated in the dampening of inflammation in IBD. It has been shown that mice null for Cd39 develop severe experimental colitis. CD39 single nucleotide polymorphisms that result in low level expression of this ectonucleotidase have been described in patients with Crohn’s disease. In humans, CD39 is expressed on Treg and on memory CD4 effector cells.

Given the key role of CD39 in immune regulation, we hypothesized that specific expression on Treg and on effector Th17 could diminish the pathogenic potential of such modified effector cells. To test this hypothesis, we generated regulatory Th17 (regTh17) cells by exposing T memory and Tregs, obtained from peripheral blood mononuclear cells (PBMCs) of 60 healthy blood donors, to IL-6, IL-beta and rTGF-beta. The phenotype of Tregs and regTh17 cells was assessed by flow cytometry, while the suppressor abilities of these cells were determined by proliferation assays and intracellular cytokine staining. The in vivo frequency of regTh17 cells (defined as IL-17 CD39high) was assessed in PBMCs and lamina propria mononuclear cells of 17 healthy subjects and 25 patients with Crohn’s disease.

When compared to Treg, regTh17 cells displayed higher CD39 expression, greater frequencies of IL-17-producing cells, comparable levels of FOXP3 and CD73 and similar inhibition over CD4 target cell proliferation and IL-17 production. In contrast to Treg, regTh17 cells were also able to suppress IFN gamma production by CD4 cells. The in vivo frequency of regTh17 cells was lower in Crohn’s patients than in healthy subjects in both peripheral blood (6.1±1.4 vs. 14.8±5.3; P=0.02) and lamina propria (36.8±9.2 vs. 64.6±9.5; P=0.055). These data suggest that in Crohn’s disease, effector Th17 cells fail to up-regulate CD39 and hence are impeded from becoming regTh17. Failure of Th17 to undergo this form of self-regulation may explain predominance of effector immune responses and consequent perpetuation of tissue damage in this and other inflammatory conditions.
Creating a Diabetes Group Visit for Brazilian Immigrants

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Our innovation seeks to address two clinical problems related to diabetes in the Brazilian immigrant population in Somerville: (1) Chronic disease management is extraordinarily difficult in the context of the traditional 15-minute appointment and (2) the difficulties are amplified by cultural barriers that make lifestyle change especially challenging for these patients. By developing and implementing a diabetes group visit for Brazilian immigrants, we hope to increase our patients’ knowledge and understanding of diabetes, improve their outlook on self-management techniques, and ultimately decrease their risk of diabetes-related complications.

Our intervention consists of a group medical visit program based on the diabetes self-management program developed at the Stanford Patient Education Research Center. We conducted focus groups of health care providers (physicians, nutritionists, community health workers, nurses, medical assistants, and social workers) working with the Brazilian community and in-depth patient interviews to modify the model to be more culturally appropriate to our target population. The program includes six 2-hour sessions in which group activities and motivational interviewing techniques are used to present an interactive curriculum on diabetes related topics. Sessions are conducted in Portuguese and staffed by a family physician, a medical assistant, and one or more students.

To evaluate our intervention, we intend to follow both quantitative and qualitative data. Quantitative data includes HbA1c, LDL, weight, blood pressure, etc. Qualitative data is based on the pre- and post-intervention responses to a patient survey measuring knowledge of and attitudes about diabetes self-management. Although the intervention is still in its pilot phase, initial results have been promising. Survey responses indicate that patients in our first cohort became more informed about their diabetes and more confident in their ability to make and maintain lifestyle changes. All involved patients lost weight during the intervention period.

Looking forward to subsequent iterations of our group medical visit program, our focus is on streamlining the curriculum, scaling up to include more patients, and potentially reaching out to patients from our first cohort to return to the clinic as peer educators.
Characterization of an ESX-Type Secretion System in *Bacillus subtilis*

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The ESX family, or Type VII, secretion systems of Gram-positive bacteria are required for the virulence of several human pathogens, most notably *Mycobacterium tuberculosis*. Gene clusters coding for ESX-type systems have also been identified amongst non-pathogenic Gram-positive organisms including the highly tractable model system, *Bacillus subtilis*. In this study, we demonstrate that *B. subtilis* codes for a nonessential homologue of the mycobacterial ESX-1 locus (*yuk*). We developed a functional secretion assay to demonstrate that each of the *yuk* gene products is required for secretion of the virulence factor homolog, YukE. Surprisingly, by quantitative profiling of culture supernatants, we find that YukE may be the sole substrate of the secretion system. Further, we begin to define the biological requirements for secretion, including a dependence on regulatory systems involved in bacterial community architectures such as biofilms. Most strikingly we identify a substrate processing event that is specific to biofilm communities. Together, our results provide not only a description of the genetic requirements of an ESX-type system in a non-pathogenic organism, but suggest that the secretion system activity may depend on the state of the bacterial community itself.

In addition to studying the components of the *yuk* operon in *B. subtilis*, we are also designing and testing constructs to determine whether the proteins from the *Mtb* secretion system can complement their counterparts in *B. subtilis*. Such a chimeric system will be used to further characterize conserved features of the ESX-type secretion system family. In addition, the ability to manipulate the *Mtb* proteins in *B. subtilis* will provide a more tractable system to study the *Mtb* secretion system directly.
Evaluation of a single visit approach to cervical cancer prevention and treatment in rural Guatemala

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In Guatemala, cervical cancer is the leading cause of cancer-related deaths among women of reproductive age (15-44 years). More than 50% of the patients diagnosed with cervical cancer die because of late detection. It is estimated that at least 75% of the women living in Guatemala’s rural areas and poor urban communities have never been screened for cervical cancer. Numerous large-scale projects in low-resource settings have demonstrated the efficacy of the “see-and-treat” single visit approach (SVA), which uses visual inspection with acetic acid (VIA) to detect abnormal cells and cryotherapy to treat precancerous lesions.

In early 2011, Partners in Health (PIH) formed the Santa Ana Women’s Health Partnership (SAWHP) in Santa Ana Huista in Huehuetenango, Guatemala. PIH helped forge a partnership among one public and two private local institutions with the goal of providing SVA services to 95% of women aged 30-50 in the municipal population of 11,000. The evaluation of this intervention consisted of a literature review, interviews with care providers, and an analysis of de-identified patient data.

The evaluation revealed that the SAWHP is reaching women who have differing levels of access to care. Half of the women seeking screening or consultation through SAWHP have received either a Pap smear or VIA (without cryotherapy) in the previous five years. However, even those with access to care had not received a service of high quality; the vast majority of these women: (1) were either not aware of the screening results or (2) never received the results in the case of the Pap smear.

The evaluation also found that the SAWHP can better target women in the 30-50 year age range. To date, 974 women have received general women’s health consults and 738 women have been screened for cervical cancer through VIA alone, but only 59% (577/974) of the women attended by SAWHP were from the target age group.

Finally, the evaluation recommends that the SAWHP investigate its low positive VIA rate. Of the 738 women screened through VIA provided by SAWHP, only 4% (28/738) were found to be positive. A VIA positivity rate of 4% is considered very low (13% positivity rate in similar low-resource settings), and may be attributable to the extensive training of the care providers or to the sampling bias of healthy women who tend to seek screening services. In the coming two years, SAWHP will focus on its outreach to the target age group women who have not sought screening even though they live close to the public health clinic.
Driving Value Into Healthcare: Plagiocephaly & Time-Driven Activity Based Costing

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Time-Driven Activity Based Costing or “TDABC” is an analytical costing system that granularly depicts resource and process utilization in business environments. Developed by Professors Steven R. Anderson and Robert S. Kaplan of Harvard Business School, the system has the ability to take a deeper look at the true cost of patient care processes. While other costing systems have looked at the material costs of delivering a service, they fail to capture additional costs associated with a service, such as the time it takes a clinician to spend with a patient, documenting notes, or researching a patient diagnosis. If “value” in healthcare is defined as patient outcome divided by cost, then driving down cost of care while maintaining or improving patient outcomes has an unrealized opportunity to drive value into healthcare processes.

As a proof of concept project, the Department of Plastic & Oral Surgery examined the diagnosis of deformational plagiocephaly. Deformational plagiocephaly is the cranial flattening of an infant’s head during the first few months of life. The condition occurs in infants either left lying in one position for an extended period of time or infants who favor tuning their head to one side, leading to a flattening of one side of the cranium. The prevalence of plagiocephaly at 6-7 weeks ranges from 16-22.1%. High demand to be seen for plagiocephaly at Boston Children’s Hospital has led to the creation of a designated plagiocephaly clinic, but a significant backlog of patients waiting to be seen still exists. Through utilizing TDABC for process evaluation and optimization, our goal was to cut down on visit-time, wait-time, and visit cost while maintaining or improving patient satisfaction.
Evaluation of the Influence of Home Visits in Altering Dental Students’ Perceptions of Individuals with Special Healthcare Needs

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Purpose: One of the most underserved populations in dentistry are individuals with special healthcare needs (ISHCN). According to a 2001 HRSA National Survey involving nearly 40,000 families with children that have special needs, the most commonly reported “needed but not received” health service was dental care. Shortage of dentists willing to treat ISHCN stems from various reasons including concerns about patient behavior, disability level, extent of treatment needs, inadequate reimbursement, and lack of dental training.

Objectives: The primary goal of our project was to improve access to dental services for ISHCN by giving future oral healthcare providers meaningful experiences and the foundational knowledge required to properly manage these patients. Our objectives were to: 1) Have at least 25 HSDM students participate in a home visit by June 2013. 2) Increase the percentage of dental students who are willing to work with individuals with special health care needs.

Methods: During two hour home visits, students had the opportunity to discuss the creative adaptations that are necessary to accommodate ISHCN and gain unique perspective on non-clinical issues ISHCN experience every day. Student participants completed pre and post-visit surveys to evaluate their willingness to work with them. The means of respondents' answers were calculated for each question and were compared to the post-visit mean score of each question. Students also wrote a narrative reflection paper of their visit. Content analyses were used to count the key themes identified in student descriptions. Families received basic oral health education on how to best maintain the oral hygiene of their child.

Results: Pre/Post- assessment surveys and reflection pieces were collected from student participants. Three home visits have been conducted in the past two months. Reflections of participatory students showed that the home visit was a powerful educational experience that exposed students to obstacles these families face as well as the adjustments they have to make to overcome these challenges. When given the statement “I would like to work with ISHCN needs as dentist”, 83 percent of participants' responses changed from “Generally Agree” to “Completely Agree” after the home visit.

Conclusions: Initial findings from surveys suggest that a single home visit with a family of a child with a disability provides insights into the family’s perspective on disability otherwise unattainable in a clinical setting. This model may serve as an innovative sustainable educational tool to increase future oral health providers’ willingness to treat ISHCN.
Identifying Key Drivers of Frequent Urgent Care Visits at the Crimson Care Collaborative Clinic at MGH-Chelsea (CCC-Chelsea)

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Frequent users of emergency room (ER) services are often medically and socially complex, and suffer from high rates of morbidity and mortality. We view the overreliance on emergency medical services as problematic for three reasons. First, the ER offers minimal opportunity for continuity and coordination of care. Second, avoidable visits to the ER may interfere with the care of patients who are acutely ill and require immediate attention, especially if those health concerns can be managed at other facilities. Third, ER visits increase the likelihood of additional laboratory testing and hospital admission, especially for chronically ill patients, which costs hospitals a considerable amount of money. Given these three reasons, it is ideal to redirect frequent ER users to care pathways that more thoroughly address the medical and psychosocial needs of these patients.

At the Massachusetts General Hospital Chelsea Healthcare Center (CHC), we are interested in developing a novel clinical protocol called the Primary Care Checklist (PC-C). The PC-C would identify and target patients at MGH-Chelsea who may be at-risk of frequent visits to urgent care. To begin developing a PC-C tailored to the patient population at Chelsea, we are conducting a qualitative investigation of the key clinical and social drivers of frequent urgent care utilization at CCC-Chelsea through semi-structured interviews. CCC-Chelsea provides high-quality psychiatric and primary care to patients without primary care providers, many of whom frequently seek care from the CHC Urgent Care facility.

109 CCC-Chelsea patients have been identified who have visited Chelsea Urgent Care at least twice, for whom translation services are available for their preferred language. Recruitment letters have been sent to all of these patients to yield an ideal sample size of 15-20 participants. Semi-structured interviews solicit information about the patients’ psychosocial, cultural, and socioeconomic contexts, how they manage their illnesses (including perceptions of the severity and complexity of their illness, and social support), reasons for visiting urgent care (including the kind of care they receive at these facilities), reasons for being without a primary care provider, and opinions on their quality of care. Seven patients have been interviewed thus far.

Each interview will be transcribed into a Microsoft Word document, and coded manually according to various themes. Themes will be extracted and formulated into 23 polarized, single-idea summary statements to be used for secondary by-person factor analysis.
Enrollment Dynamics in Medicare Advantage

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Medicare Part C, known as Medicare Advantage since 2003, was established in the 1980s to enable beneficiaries to receive Medicare benefits through private health plans as an alternative to traditional fee-for-service Medicare. Under Medicare Advantage (MA), Medicare pays participating private plans a capitated risk-adjusted amount per enrollee to supply all benefits provided under Parts A and B.

The Medicare Modernization Act (MMA) of 2003 significantly changed the payment structure for MA plans. The act required the program to begin risk-adjusting payments to plans and introduced a bidding system to determine payment levels. The MMA also authorized Medicare Part D prescription drug coverage, which has become a standard component of many MA plans since 2006. The effect of these policy changes on MA enrollment has not yet been fully described. The provisions of the MMA altered the appeal of the various MA options available; studying the enrollment dynamics resulting from these changes provides insight into the factors underlying the current status of the program, in anticipation of enrollment changes that may result from the implementation of the 2010 Affordable Care Act. In this study, we characterized recent trends in enrollment in Medicare Advantage based on enrollee, contract, and market attributes.

The data sources analyzed were the Medicare Managed Care (MMC) State/County Penetration Files for 1993 to 2012, the MMC Monthly Enrollment by Contract Files for 2003 to 2012, and contract-level HEDIS data for 2003 to 2009. We intend to estimate logistic regression models to identify which enrollee, contract, and market characteristics predict MA enrollment. The characteristics used to analyze MA enrollment will include contract size, time since market entry, tax status, affiliation, market share, and MA penetration in the market in question. They will also incorporate demographic information and estimates of the competition contracts face.

Our preliminary work has focused on describing these attributes for the time period to be studied. We found that MA enrollment grew substantially from 2.67 million enrolled beneficiaries (7.5% of those eligible) in 1993 to 12.2 million enrolled beneficiaries (25% of those eligible) in 2011. Most of this growth occurred post-2005, after the MA payment changes from the MMA were implemented. 56.5% of this growth occurred in counties with above-average MA market penetration. Additionally, the majority (63.5%) of this growth occurred in plans in existence for more than five years. Further analyses will assess how MA enrollment changes have varied by enrollee, plan and market characteristics.
Improving Quality of Reporting and Performance: Clinical Significance of Coronary Artery Calcifications on CT Pulmonary Angiograms

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In patients with suspected pulmonary thromboembolism (PTE), coronary artery calcification (CAC) could be an incidental finding in CT pulmonary angiograms. In these patients, acute coronary syndrome (ACS) is a differential diagnosis. Here, we aimed to evaluate the value of CAC for prediction of ACS in these patients.

This study was approved by our institutional review board. We reviewed data from 469 consecutive patients suspected for PTE, who were referred for CT pulmonary angiography. CT scans were assessed for CAC and patients’ data on past medical health; ACS and PTE diagnosis were recorded. The association of CAC with ACS was assessed in different subgroups of patients. We also examined radiology reporting patterns of CAC in findings and impression.

About 11.1% of patients had PTE and 43.8% (206 patients) had CAC. Of these 206 records, 108 (52.4%) had CAD reported in the findings of the radiology report, and 9 out of 206 (4.4%) had CAD reported in the radiology report’s impression. Of the 98 patients with CAD on CT examination without CAD reported in the findings, 83 had no prior history of CAD in a search of the patient’s electronic medical record. In patients with ACS, CAC was significantly higher that those without (56.2% vs. 40.4%; OR=1.9). There was a strong positive association between CAC and ACS in young (age ≤ 45 in men, age ≤ 55 in women) patients (OR=3.5) and those without cardiometabolic risk-factors (OR=3.8). In patients with age ≥ 70, CAC was significantly associated with lower chance of ACS (OR=0.25). These associations remained significant after multiple adjustments for different variables including age, gender and past medical health. There was no association between ACS and CAC in patients with past history of coronary artery disease (CAD) or positive PTE.

This study provides information for radiologists and clinicians to have an assessment of ACS risk, based on CT pulmonary angiograms in suspected PTE patients. CAC is a significant predictor of ACS in younger patients and those without past history of CAD and cardiometabolic risk-factors. Our results also suggest that incidental CAD on CTPE is underreported in the findings and impression of radiology reports and that a portion of cases that are not reported include potential new diagnoses of CAD.
Needs Assessment of Medical Imaging Services and the State of Medical Imaging Technology in Haiti, Rwanda, Uganda, and Cambodia

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Because the prevalence of non-communicable diseases continues to advance and infectious diseases and disaster response also remain crucial, radiology technology and interventions are key health infrastructure facets for nations that are developing health care systems. Unfortunately, the status of radiological equipment and interventions in developing countries is often poor. Resources are always constrained, so we created a needs assessment survey to create a map of the radiology capacity of countries. The needs assessment survey included questions about operations, interest in teleradiology partnerships, radiology personnel, and following types of equipment: x-ray, fluoroscopy, angiography, mammography, ultrasound, computed tomography, magnetic resonance imaging (MRI), and nuclear medicine units.

We piloted the survey on fourteen respondents that included respondents from Malawi, India, Ethiopia, Uganda, Nepal, Ecuador, Haiti, and the United States amongst others. All respondents did not answer each question. 11 respondents expressed an interest in forging teleradiology partnerships. Of 6 respondents, 2 had access to computed tomography. All 6 had access to ultrasound. 2 had access to mammography. Of 8 respondents, all 8 had access to x-ray machines. Of 7 respondents, 3 had access to fluoroscopy. Of 6 respondents, 2 had access to angiography. Of 5 respondents, only 1 had access to MRI and nuclear medicine units. 8 of 10 respondents referred patients outside of their facilities for radiology services. The most commonly listed reason for referring to an outside facility was a lack of equipment/modality.

Our results demonstrate that valuable information can be obtained from a needs assessment survey directed towards understanding equipment needs and teleradiology interest. Our results suggest that outside facilities often lack equipment, which leads to referral to outside sources for radiology needs. In addition, there is substantial interest in forging teleradiology partnerships, which Massachusetts General Hospital Imaging Global Health Programs could help to address. Future directions should include surveying the following nations: Haiti, Kenya, Uganda, Cambodia, and Rwanda.
Non-endothelial origin of midpalatal suture osteoblasts

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It has long been recognized that mechanical stress modulates proper postnatal skeletal development by influencing bone formation (Martin 2000). This process called mechanotransduction is observed in cranial sutures and results in increased osteoblast function and bone formation in the suture. In syndromes such as craniosynostosis, premature closure of cranial sutures due to early bone apposition inhibits normal bone formation and response to mechanical stress (Melville, Wang et al. 2010). Consequently, patients present with abnormally shaped skulls caused by the increased intracranial pressure from the growing brain.

Studying the cellular responses to mechanical force contributes to our understanding of bone as well as cellular biology and may provide molecular targets for future craniosynostosis therapy development. However, there is a gap in knowledge regarding the origin of the osteoblasts in cranial sutures. Recent evidence suggests that populations of osteoblasts may be derived from endothelial cells, however, this has not been demonstrated in cranial facial bones (Medici, Shore et al. 2010). Our hypothesis is that endothelial cells located around or within the suture undergo endothelial-to-mesenchymal transition and subsequently differentiate into osteoblasts.

To test this hypothesis, we utilized the mouse midpalatal suture expansion model that uses prolonged external force to enhance sutural development and bone formation (Hou, Fukai et al. 2007). These transgenic mice contained a Cre recombinase gene under the VE-Cadherin promoter and a Td-Tomato gene that requires Cre-mediated recombination for expression. Immunofluorescent staining revealed that all Td-Tomato positive cells also expressed the endothelial marker CD31. However, there was no colocalization between Td-Tomato and osteoblast specific Osterix signal. Therefore, our study suggests that osteoblasts in the midpalatal suture of mice do not have endothelial origin.
Detecting inflammation: *E. coli* sensors of reactive oxygen species

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Inflammation is ubiquitous in both health and disease. When properly controlled, inflammation helps resolve infections and repair damaged tissue. But when dysregulated, inflammation can cause disease. The complexity of inflammation is illustrated by the varied diseases it contributes to, from atherosclerosis to cancer. In light of this complexity, there is a need for a variety of strategies to monitor and study inflammation.

In this project, we focus on detecting reactive oxygen species (ROS) as a marker of inflammation. At sites of inflammation, inflammatory cells may be stimulated to release ROS. This helps sterilize a wound, but can also cause tissue injury. Thus, extracellular ROS is likely to be a useful marker for severity of inflammation.

Current ROS detection methods are based on small molecules that fluoresce when oxidized. However, these small molecules are often nonspecific; they respond to a variety of different ROS. These small molecules are also not suitable for *in vivo* use.

In an effort to address the limitations of current ROS detection methods, we chose to engineer *E. coli* to detect ROS using the redox-responsive transcription factors OxyR and SoxR. We hypothesized that we would be able to make ROS-specific sensors using OxyR and SoxR since they are known to coordinate distinct responses to hydrogen peroxide and superoxide, respectively. This bacterial approach may also enable *in vivo* monitoring of inflammation, especially for gut conditions like inflammatory bowel disease.

Thus far, we have built and tested a number of different circuit designs based on SoxR and OxyR. Using flow cytometry, we are able to quantify the fluorescence of populations of cells exposed to defined concentrations of ROS. We have experimented with different circuit topologies (positive feedback, open loop) and different circuit components in an effort to achieve high specificity and wide input and output dynamic ranges.

We have identified the soxS and oxyS promoters as the best binding partners for SoxR and OxyR respectively. Preliminary results from these circuits indicate that positive feedback circuit designs produce greater output than open loop designs, but have higher background and thus a lower output dynamic range. Positive feedback and open loop circuits appear to have similar input dynamic ranges, suggesting that the input dynamic range is dependent on the ROS-sensitive transcription factor rather than the circuit topology.

Future work includes further characterization of the circuits, followed by *in vitro* testing with cultured macrophages and finally, testing in mouse models of colitis.
Developing a Comprehensive Survey of Maternal and Child Health Seeking Behaviors among Women in Rural Liberia

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Liberia is a remote West African nation working to reverse the after-effects of a 14-year civil war. Alternating waves of sectarian fighting have left serious gaps in the government’s ability to deliver public services now that peace has been established. The targeted destruction of clinics and hospitals has resulted in low national health statistics, including a maternal mortality ratio of 990/10,000 and a neonatal mortality rate of 32 per 1000 live births. Rural residents of Liberia bear the brunt of such health disparities. Clinics are widely spaced and poorly equipped, necessitating long walks and significant expenses for sick patients in need of care.

Tiyatien Health (TH) is a registered 501(c)3 non-profit organization that has been working in rural Southeastern Liberia since 2007. The organization’s goal is to increase the availability of quality healthcare in the region, particularly focusing on conditions not covered by government services, such as HIV/AIDS and epilepsy. Recently, TH has developed an interest in maternal and child health, as this is an area where disparities between remote and metropolitan regions of the country are severely pronounced. However, detailed information on the healthcare seeking behaviors of pregnant women and mothers in Southeastern Liberia is lacking. To address this lack of data we worked to develop a comprehensive survey on maternal and child health that could be administered by local surveyors with limited literacy. We researched internationally validated survey tools such as the MEASURE Demographic and Health Surveys as our primary sources for relevant questions. We adapted these questions to the Liberian cultural context, and translated them into Liberian English (the local dialect) with the help of our local staff. Our final output was a 100 question survey that covered the following eight topics: Demographics, Water/Sanitation, Health System Access, Reproductive History, Family Planning, Maternal Health Indicators, Neonatal Health Indicators, and Child Health Indicators.

The survey was administered via a two-stage randomized cluster sample to new mothers (defined as women who had given birth in the last 5 years) throughout Konobo District, Liberia. Approximately 600 surveys were administered by a team of 8 Liberian surveyors and 3 supervisors over the course of 5 weeks. Data analysis is ongoing.

Limitations: Recall bias may result in relative over-reporting of health and access issues among women who have had adverse birth outcomes or whose children have had serious illnesses.
Fabrication of Blended PCL/PLGA/β-TCP Scaffold as a Guided Bone Regeneration Membrane

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Guided bone regeneration (GBR) is a procedure that is widely used in dental practice to restore the alveolar bone mass in patients when horizontal and vertical dimensions of the alveolar ridge are not sufficient for dental implants. Both polycaprolactone (PCL) and poly(lactic-co-glycolic acid) (PLGA) are biomaterials that are often used in tissue engineering scaffold applications. In this study, a bio-absorbable guided bone regeneration membrane composed of blended PCL, PLGA and beta-tricalcium phosphate (β-TCP) was developed using the solid freeform fabrication (SFF) technology. PCL/PLGA membranes were also fabricated using the same method for a comparison group. The physical properties of the membranes were evaluated using the field emission scanning electron microscopy (FE-SEM). Dental pulp stem cells were then seeded on both PCL/PLGA/β-TCP and PCL/PLGA membranes, and were incubated at 37°C under the osteogenic medium. To evaluate the differentiation of DPSCs, Real-Time PCRs were performed for osteogenic markers including RUNX and ALP on Day 28. Alizarin S Red Staining was also performed in order to evaluate the calcium deposition level of the cells. The In vitro cell activity assays revealed that the osteogenic differentiation of seeded DPSCs were significantly promoted by the PCL/PLGA/β-TCP membranes in comparison to PCL/PLGA membranes. In addition, the pH results indicated that PCL/PLGA/β-TCP membranes produced a significantly less acidic environment than PCL/PLGA membranes. Further studies including a carefully designed in vivo experiment are needed in order to test the feasibility of PCL/PLGA/β-TCP membrane in the application of guided bone regeneration.
Obesity and Age at Diagnosis Impact Quality of Life and Long-Term Outcomes in Psoriasis Patients

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Psoriasis is a chronic, inflammatory skin disorder that imposes physical and psychosocial burdens over a patient’s life course. Psoriasis may begin at any age and is known to associate with obesity. The purpose of this study was to evaluate the impact of body mass index (BMI) and age at diagnosis on the socioeconomic status, medical co-morbidities, psychosocial outcomes, and current and chronic quality of life (CQoL) of psoriasis patients.

114 psoriasis patients were examined and asked to complete a self-administered questionnaire regarding disabilities, relationships, education, as well as medical and economic outcomes (a smaller subset of 58 subjects also answered questions regarding religion and discrimination). Participants also answered the ten questions used in the standard Dermatology Life Quality Index (DLQI) modified to ask “over the last week,” “over the last year,” and “over your lifetime with psoriasis.” Survey responses were compared amongst the patients based on BMI (normal, overweight, obese) and age-at-diagnosis quartile.

Patients with elevated BMI were more likely to rate their general health lower (P<0.001), believe that their psoriasis had caused their weight gain (P=0.014), experience sleep problems over their lifetime (P=0.016), hide their psoriasis over their lifetime (P=0.010), have their self-confidence affected by their psoriasis over their lifetime (P=0.011), and avoid common activities over their lifetime (P=0.012). Those diagnosed at a younger age were more likely to have felt depressed (P=0.003), believe that their psoriasis had caused their depression (P<0.001), experience sleep problems over their lifetime (P=0.004), use recreational drugs (P<0.001), hide their psoriasis over their lifetime (P<0.001), and experience more severe discrimination in social settings over their lifetime (P=0.002). A greater lifetime Dermatology Life Quality Index (LT DLQI), which was measured using an adjusted form of DLQI, was significantly associated with younger age at diagnosis (P<0.001).

A limitation of our study is that our sample may not be representative of the general population with psoriasis because three-quarters of our patients received a college degree and the majority was Caucasian. However, in this group of psoriasis patients, we found that there are long-term negative effects of elevated BMI that impose additional burdens on psoriasis patients, including impairments in sleep quality and increased social anxiety. In addition, our study suggests that early-onset psoriasis is associated with lifetime negative effects, including depression, sleep problems, recreational drug use, concealment of one’s disease, discrimination, and greater LT DLQI.
Action for Children and Teenagers In Oral health Need (A.C.T.I.O.N.)

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The Actions for Children and Teenagers In Oral health Need (ACTION) Program is an ongoing project in which HSDM pre-doctoral dental students provide dental treatment to pediatric patients once a month under the supervision of an attending pediatric dentist. This project serves the low-income, minority families of the community located in the eastern section of Cambridge, MA. Since caries is the most prevalent disease among children of low socio-economic status, it is imperative that these vulnerable children be provided access to oral healthcare. The Windsor Street Dental Clinic (WSDC) is a component of the Cambridge Health Alliance (CHA), the only public health hospital and safety net group in Massachusetts.

The ACTION Program operates one Saturday per month at CHA’s Windsor Street Dental Clinic. There are 7 dental operatories in the clinic, and with the help of ACTION volunteers, all seven chairs are fully functioning at each session. Each session is composed of an attending dentist, CHA staff, and 17 HSDM volunteers. The purpose of each session is to provide various dental treatments to the pediatric patients of the clinic under the supervision of the attending pediatric dentist. The ACTION Program not only aided in the clinic’s survival through harsh economic conditions, but also it also has augmented the clinic’s Saturday pediatric capacity. The capacity has increased by 200%.

The collaboration among Harvard School of Dental Medicine, Cambridge Health Alliance, and patients within the local community is designed to benefit all stakeholders. Through this project dental students are exposed to dental public health in a real-life setting and given the experience to develop their skills in the treatment and management of pediatric patients. Furthermore, it provides parents within the surrounding low-income community a convenient way to access dental care for children.

Since July 2009 to Oct 2012, the ACTION Program has had over 30 clinic sessions providing dental treatment to hundreds of pediatric patients totaling over 750 appointments. Volunteers for the programs have provided more than 400 comprehensive exam & dental prophylaxis, 80 composite/temporary restorations, 200 sealants, 20 pulpotomies and stainless steel crowns, and 45 extractions. With continuously successful and productive clinic sessions, the ACTION Program at Windsor Street Health Clinic benefits the whole community.
SMAD1 and GATA1 Protein Interactions in the Myeloid Lineage

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The regeneration of blood cells underlies the recovery of patients suffering from hematologic challenges such as irradiation and hematopoietic stem cell transplantation. Cell signaling pathways have been shown to be integral in the process of hematopoietic regeneration, but their complete roles are not fully understood. For example, the SMAD family of proteins, of which SMAD1 is a member and a focus of this project, mediates the effects of BMP signaling; it has been shown that SMAD1 plays a role in post-traumatic erythropoiesis. Recently, it was also demonstrated that lineage regulators can direct binding of signaling factors to lineage-specific regions of the genome. GATA1, an erythroid lineage regulator, and SMAD1 ultimately co-occupy erythroid promoter regions in the process of hematopoietic regeneration. We hypothesize that GATA1 and SMAD1 interact, either directly or via other protein partners, which leads to their co-occupation of genomic sites. Therefore, to identify potential protein complexes of GATA1 and SMAD1, we aimed to over-express each factor in an erythroleukemic cell line followed by immunoprecipitation and mass spectroscopy. To create stable cell lines with inducible overexpression, FLAG-tagged SMAD1 and GATA1 cDNA were inserted into separate doxycycline-inducible lentiviral vectors. The SMAD1 and GATA1 lentiviral constructs were transfected in to erythroid cells and individual clones were selected, ultimately yielding inducible SMAD1- or GATA1-overexpressing stable cell lines. In addition, erythroid cell lines constitutively overexpressing either SMAD1 or GATA1 were employed in complementary experiments. For SMAD1 overexpression, a SMAD1 construct was obtained and used to directly transfec erythroid cells. Successful clones were isolated, SMAD1 expression confirmed, and stable lines expanded. In parallel, using a stable line of GATA1-overexpressing erythroid cells obtained from Stuart Orkin’s lab, BMP4 stimulation induced nuclear localization of SMAD1 and nuclear extracts were isolated. To allow for the presence of multiple GATA1 complexes, the nuclear extracts were fractionated to separate complexes by size: GATA1 was identified in two distinct sets of fractions, suggesting its presence in at least two complexes. SMAD1 was also identified in these fractions. Immunoprecipitation of GATA1 from these fractions followed by mass spectroscopy will identify proteins interacting with GATA1. Likewise, immunoprecipitation of SMAD1 from the SMAD1-overexpressing cell lines and subsequent mass spectroscopy will identify SMAD1 interacting partners. In combination, these two approaches will paint a complete picture of the GATA1- and SMAD1-containing complexes found in a progenitor erythroid lineage. Future directions include examining the dynamic binding patterns of GATA1 and SMAD1 through different states of differentiation and in different cell lineages.
The Role of the Renal Tubular Epithelial Cell in Kidney-Induced Cardiac Allograft Tolerance

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Currently, graft half-life for heart allograft recipients is 9.9 years. A chronic state of immunosuppression and drug-related side effects are responsible for most of the mortality. Mixed chimerism, a state in which the recipient’s immune system is partially replaced by the donor’s, presents an alternative to immunosuppression. A protocol for the induction of mixed chimerism in human kidney allograft recipients was introduced in 1998. Some patients in that trial have survived more than 10 years with excellent renal function off all immunosuppression. Mixed chimerism is the only approach to tolerance induction in human kidney recipients that has proven successful.

In contrast, the same mixed chimerism protocol is unsuccessful in nonhuman primate (NHP) recipients of heart allografts. However, co-transplantation of a kidney with a heart from the same donor does induce stable tolerance in NHPs. Although the chimeric state is eventually lost in NHP and human recipients, tolerance is maintained through peripheral mechanisms hypothesized to include T regulatory (CD25+FoxP3+) cells (Tregs).

We attempted to elucidate the mechanism responsible for kidney-induced cardiac allograft tolerance (KICAT). Renal tubular epithelial cells (RTECs) are immunologically active, and we hypothesized that these kidney-specific cells could contribute to tolerance induction. We first determined whether stimulated RTECs secrete TGFβ, a cytokine important for Treg development. We added IFNγ and/or TNFα to culturing RTECs (10,000 u/mL of each cytokine). After 14 days, supernatant from untreated RTEC cultures contained 192.4 pg/mL of TGFβ. RTECs treated with IFNγ produced 190.3 pg/mL and cells treated with TNFα produced 291.3 pg/mL. RTECs treated with both IFNγ and TNFα produced the highest concentration TGFβ at 362.9 pg/mL.

We next attempted to expand Tregs using the RTEC supernatants. Supernatant from preliminary experiments containing TGFβ (276.6 pg/mL) was added to peripheral blood mononuclear cell (PBMC) cultures. After 5 days, 3.6% of CD4+ cells were CD25+FoxP3+ in the supernatant treated group compared to 0.4% in the control containing culture media in place of supernatant. We repeated the experiment co-culturing RTECs with purified CD3+CD25+ T cells. After 5 days, 46.2% of CD4+ cells were CD25+FoxP3+ compared to 7.5% in the control containing no RTECs.

These data demonstrate the ability of RTECs to secrete TGFβ and suggest that RTECs and/or soluble mediators they release can expand Tregs. RTECs could represent the mechanism by which a kidney confers tolerance to a co-transplanted heart allograft. Next, we will demonstrate whether expanded Tregs are capable of donor specific immune suppression in vitro.
Myeloid cell recruitment is necessary for bio-engineered vessel formation with ECFCs and MPCs in ischemic muscle

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All organs and tissues require a healthy vascular network for oxygen and nutrient delivery as well as elimination of waste products. Building vascular networks is important for the generation of thick three-dimensional cell-based bioengineered constructs, as well as the establishment of new blood supply in ischemic tissues.

Previous studies have shown that coimplantation of human endothelial colony forming cells (ECFCs) and mesenchymal progenitor cells (MPCs) isolated from blood or bone marrow into immunodeficient mice results in the formation of extensive vascular networks by day 7. Subsequent studies have shown that the recruitment of myeloid cells, soon after ECFCs/MPCs injection into immunodeficient mice, is necessary for blood vessel formation by ECFCs/MPCs in Matrigel implants. We hypothesize that recruitment of myeloid cells is necessary for blood vessel formation by ECFCs/MPCs in an ischemic setting and improves blood flow in ischemic tissues.

Hindlimb ischemia was generated by ligation of femoral arteries and veins. Subsequently, ECFCs/MPCs were injected into the ischemic muscle. Blood flow measured by laser Doppler showed better recovery in the ECFCs/MPCs injection group compared to the control. Ischemic muscle tissue was harvested and fluorescence-activated cell sorting (FACS) and immune-staining were conducted.

FACS data showed there was an increase in CD11b-positive myeloid cells, Ly-6G-positive neutrophils, and F4/80-positive macrophages recruited at day 2 in hind limb tissue with ECFCs/MPCs injection when compared to Matrigel injection. Interestingly, neutrophils declined by day 7, while the number of CD11b-positive myeloid cells and macrophages did not. I further demonstrated this dynamic phenomenon of myeloid cell recruitment using immunohistochemistry (IHC) with antibodies specific for CD11b, Ly-6G, and F4/80, together with Ulex europaeus agglutinin (UEA), lectin specific for human endothelial cells. To confirm the role of host myeloid cell recruitment in blood vessel formation by ECFCs/MPCs, Gr-1 antibody was administered every 2 days starting 2 days prior to femoral artery and vein ligation and throughout 7 days of hindlimb ischemia in order to deplete host myeloid cells. Laser Doppler measurement revealed that depletion of myeloid cells blocked the improved blood flow recovery in ECFCs/MPCs injection group.

Our data suggest that host myeloid cells contribute importantly to the new blood vessel formation by ECFCs/MPCs in ischemic muscle. Better knowledge of myeloid cell recruitment in blood vessel formation may enable future developments in the bioengineering field by allowing in situ ischemic tissue and tissue-engineered organs to receive adequate perfusion at a faster rate.
Cognition and the Take-up of Subsidized Drug Benefits by Medicare Beneficiaries

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Medicare Part D enrollees with limited income and resources can qualify for a low-income subsidy (LIS) that provides premium and cost-sharing assistance to reduce out-of-pocket costs for prescription drugs. Take-up of the LIS by eligible beneficiaries who must apply for it has been low despite the attractive drug coverage it offers at no cost to beneficiaries and the outreach efforts by the Social Security Administration. Seniors with cognitive deficits may be particularly prone to making poor enrollment decisions. However, whether LIS take-up is related to cognition is unknown.

We analyzed nationally representative survey data from the Health and Retirement Study on low-income elderly Medicare beneficiaries who were likely eligible but did not automatically qualify for the LIS. Using survey assessments of overall cognition and numeracy, we examined how cognitive abilities were associated with Part D enrollment, awareness of the LIS, and application for the LIS reported by these eligible beneficiaries from 2006 to 2010. We also compared out-of-pocket drug spending and premium costs between those who did and did not report receipt of the subsidy. Analyses were adjusted for sociodemographic characteristics, household income and assets, health status, and presence of chronic conditions.

Lower cognition and numeracy scores were strongly associated with lower rates of reported Part D enrollment (P≤0.03) and LIS application (P≤0.002). Compared with LIS-eligible beneficiaries in the top quartile of overall cognition, adjusted rates of Part D enrollment, LIS awareness, and LIS application were 5.8%, 17.1%, and 9.3% lower for those in the bottom quartile, respectively. Reported receipt of the LIS was associated with significantly lower annual out-of-pocket drug spending (adjusted mean difference: −$256; P=0.02) and premium costs (−$273; P=0.02).

Among Medicare beneficiaries who were likely eligible for the Part D LIS but had to apply, poorer cognition and numeracy were associated with lower take-up. In addition, those who reported applying for and receiving the subsidy had lower out of pocket and premium costs. Current educational and outreach efforts encouraging LIS applications may not be sufficient for beneficiaries with limited abilities to process and respond to information and additional policies may be needed to extend the financial protection conferred by the LIS to all eligible seniors. More generally, this evidence suggests policies that rely on seniors’ choices to support efficient competition among plans may be less effective when not coupled with government efforts to regulate choice sets and guide beneficiaries to the best available options.
Salivary Biomarker Development for Detection of Pre-Diabetes

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25.8 million children and adults in the United States (8.3% of the population) have diabetes and a large number (7 million) is diagnosed only after they have complications. More than 79 million Americans (25.4%) have pre-diabetes, with the highest prevalence in Puerto Ricans and other Hispanics. Obesity is a strong risk factor for type 2 diabetes and pre-diabetes. This project tests the hypothesis that salivary biomarkers can be developed and used to detect pre-diabetes in an overweight and obese Hispanic population. Saliva is a multi-constituent biofluid reflective of physiological status. Unlike other body fluids, salivary diagnostics offer an easy, inexpensive, safe and non-invasive approach, and may provide a means of screening for and/or detecting early stages of diabetes.

This study focuses on the selection and verification of salivary biomarkers that were previously discovered to detect pre-diabetes, the precursor of type 2 DM, in a Puerto Rican cohort. The discovery study used 20 pre-diabetic and 20 type 2 DM patients that were matched based on age, gender, hypertension, non-smoking, BMI, and no medication. The objective was to select candidates and verify the salivary transcriptomic biomarkers that can discriminate for pre-diabetes and type 2 DM.

Salivary biomarker verification is based on the PRoBE (prospective-specimen-collection and retrospective-blinded-evaluation) design. The Affymetrix HG U133 Plus 2.0 Array (Affymetrix, Santa Clara, CA) was used to profile transcriptomes and discover altered gene expression in saliva supernatant. 25 biomarkers candidates discovered from the microarray study were selected for verification by quantitative PCR (qPCR).

The qPCR data are yet to be analyzed to determine if the level of expression of which mRNA biomarkers is significantly different (P < 0.05) between pre-diabetes and type 2 DB and whether they are up-regulated or down-regulated. Once found, their sensitivity and specificity will be determined based on a receiver operating characteristic plot.

Only 20 samples for pre-diabetes and type 2 DM, respectively, were used for discovery and verification of transcriptomes. Generalizability of the test result has not yet been determined.
Induction of C/EBP-beta by Fibroblast Growth Factor 21 in Mouse Liver

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Obesity is a growing concern in the US as over one third of adults are obese and the trend has been rising over the past two decades. One possible therapeutic agent that has emerged recently is Fibroblast Growth Factor (FGF21), a member of the endocrine FGF family which regulates energy homeostasis through its effects on hepatic metabolism and insulin sensitivity. The administration of intracerebroventricular hFGF21 in obese mice has led to increased whole-animal energy expenditure and body temperature through alterations in gene expression of critical metabolic regulators, including changes to a member of the CCAAT Enhancer Binding Protein family, C/EBP-beta. C/EBP-beta exists in three isoforms, two active forms (LAP* and LAP) and one truncated inhibitory form (LIP). Both the quantity and ratio of the three isoforms of the transcription factor are involved in glucose regulation and adipogenesis. Studies have found that a decrease in the ratio of the active and inhibitory isoforms (LAP to LIP ratio) leads to a decrease in adipose mRNA level.

Based on these previous studies, we hypothesized that the induction of intracerebroventricular hFGF21 leads to a change in ratio C/EBP-beta in peripheral tissues. Mouse liver tissue was chosen for this study because of the high expression of C/EBP-beta and the essential role of adipose and glucose regulation in the tissue. Western blot and qPCR were used to analyze FGF21 protein and gene levels of mouse liver from mice infused with hFGF21 for seven days into the lateral ventricle of the brain. There was an increase in LAP (p=0.0024) and LIP (p=0.029) but no increase in the largest isoform (LAP*). Central FGF21 also appears to decrease LAP:LIP ratio in mouse liver, consistent with our hypothesis that FGF21 infusion leads to a change in C/EBP-beta ratio, resulting in a decrease in adipogenesis and increase in energy metabolism. In addition, cell culture studies with 3T3-L1 mouse fibroblast cells were performed to study the mechanism of C/EBP-beta induction by FGF21. To determine whether this induction was STAT3 regulated, cells were treated with hFGF21 alone or with hFGF21 and STAT3 inhibitor for 48 hours. Preliminary data suggested that the induction of C/EBP-beta by FGF21 in cells was reduced by STAT3 inhibitor. Future studies are required to determine the expression of C/EBP-beta in other tissues and confirm the role of STAT3 in the mechanism of change in C/EBP-beta expression by FGF21.
A Retrospective Review of Outcomes with the Codman Bactiseal Universal Shunt versus the Chhabra Shunt

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There are over 100,000 new infant cases of Hydrocephalus in sub-Saharan Africa every year. The annual economic burden is estimated at up to $56 billion. CURE Children’s Hospital of Uganda (CCHU) currently treats around 300 children for hydrocephalus each year, half of which receive the Chhabra shunt. At CCHU, the infection rate within the first year of insertion was 11.8% for the first 500 shunts implanted, and infection was the single most common cause of shunt failure. The occurrence of a shunt infection has multiple adverse effects, including death, brain damage, prolonged hospitalization, and increased hospitalization costs. Reducing the infection rate would be a major improvement in the care of children with hydrocephalus.

The Codman Bactiseal shunt is a silicone shunt impregnated with 0.15% clindamycin and 0.54% rifampicin. Data from the UK Shunt Registry of 715 patients receiving Bactiseal shunts had 16 shunt infections vs. 31 infections in 715 non-Bactiseal control shunts, p=0.04. However, the microorganisms that typically cause shunt infection in Uganda have been shown to differ from those typically present in developed settings. Therefore, there is need to evaluate the effectiveness of the Bactiseal shunt in reducing shunt infections among CCHU’s patients.

From October 2011 to February 2012, 82 sequential shunt patients at CCHU received the Bactiseal shunt. We compared the 6-month outcomes for these patients with those of the 82 patients that immediately preceded them and received the Chhabra shunt (May to October 2011). We defined shunt failure as patient death or neurosurgical intervention to revise/replace the shunt within six months. Outcome was determined by follow-up visit, communication with the parents, or home visit.

Preliminary data shows a non-significant (p=0.33) trend towards a lower rate of shunt failure among Bactiseal patients. Currently we have 6-month follow-up for 72/82 (87%) of Chhabra and 56/82 (68%) of Bactiseal patients. Shunt failure rates for patients with 6-month results are currently 26/72 (36%) for Chhabra and 18/56 (32%) for Bactiseal. It is anticipated that a disproportionate number of the patients that experienced shunt failure were found early in follow-up and that rates of shunt failure will decrease with ongoing follow-up.

It is likely that our analysis will show a trend towards a reduced rate of shunt failure among patients that received a Bactiseal shunt, but that this difference will not be statistically significant. This warrants further investigation with a randomized controlled trial which is currently in planning.
Religion and Spirituality as Predictors of Dental Anxiety

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Dental anxiety is a serious issue that affects a significant portion of the population. An estimated 11.6% of the population suffers from high dental anxiety (score > 19 on Modified Dental Anxiety Scale). A much larger portion of the population has some level of dental anxiety (as much as 60%). Dental anxiety is related to a reduced frequency of dental visits and subsequently oral health complications. Additionally, dental anxiety has been elucidated to contribute to negative psychosocial effects. The ability to alleviate the problem of dental anxiety would greatly improve the oral health, as well as mental health, of a significant portion of the population.

A considerable body of research suggests that religion and spirituality are important factors in psychological health, stress, and treatment. I therefore studied the effects of religion and spirituality on dental anxiety in particular.

I hypothesize that, within the Jewish framework, high levels of spirituality and religiosity ameliorate, to a certain extent, dental anxiety. This is based on the Jewish belief that G-D takes care of each individual and does for everyone what is appropriate for them. It is still each individual’s responsibility to take care of themselves as best as they can. I believe this outlook can decrease dental anxiety, or at least increase the frequency of dental visits amongst anxious patients. Believing that G-D is looking out for someone and doing what is in their best interest can reduce fear. Additionally, feeling that it is one’s spiritual obligation, not only their physical obligation, to care for their health can promote dental visits despite anxiety.

Discovering this relationship can provide potential ways of addressing this issue. Perhaps dental anxiety can be overcome by promoting spiritual awareness. By tapping into a patient’s spiritual beliefs, or educating them about this concept, their dental anxiety can be reduced. (As previously stated, I am currently only speaking in regard to Judaism. I do not claim to know the beliefs of other faiths.)

To test my hypothesis I will administer three online questionnaires. The Modified Dental Anxiety Scale will be used to assess dental anxiety; The Spiritual Health Locus of Control will be used to assess spirituality; and a self-designed survey to assess frequency of dental visits. The data will be analyzed to determine if there is a correlation between religion/spirituality and dental anxiety. The study has yet to be concluded and results cannot be reported.
Optimizing the Role of Academia in Regulatory Medicine

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There is growing concern within the biomedical research community that we do not effectively translate ideas from the research laboratory to the patient. If it continues to cost too much and to take too long to discover and develop new medicines, we will miss a golden opportunity to capitalize on our rapidly growing knowledge about normal and disease states. It is critical for academic institutions like Harvard Medical School to divine new approaches to collaborate with the pharmaceutical industry, as well as government agencies like the FDA, to develop, manufacture, evaluate, and monitor the safety and efficacy of novel therapies.

Our goal was to describe the current mode of interactions between the three sectors of academia, industry, and FDA. We aimed to identify current challenges to collaborations across these sectors, as well as the skills and tools that academia can uniquely contribute to address these challenges and play an expanded role in the future of regulatory science.

We interviewed 13 experts: 6 from academia, 5 from FDA, and 2 from industry. Many of these individuals had moved between these sectors over the course of their careers, and were able to comment on their experiences in multiple different capacities. The interviews lasted 30-60 minutes, and were analyzed qualitatively to identify both common themes and conflicting viewpoints.

There was general consensus among the interviewees on several areas in which academia can contribute greatly to regulatory science. These included definition of novel molecular targets and biomarkers, toxicology, and informatics for post-marketing surveillance. Moreover, particular strengths attributed to academia were neutrality, freedom from profit-seeking (unlike industry) and freedom from political bureaucracy (unlike FDA). Experts noted that this might enable academia to be a neutral ground for all three parties to come together and have open communications.

There was also consensus across sectors that academics are frequently undertrained in clinical, translational, and regulatory science. Moreover, incentives and rewards in academic culture (grants, funding, promotion, and tenure) are not structured so as to encourage individuals to enter and advance these fields, compared to the basic sciences. Particularly on issues of scholarly publication, many experts expressed frustrations that the agendas and interests of different parties often directly conflicted. Therefore, the academic agenda needs to be reprioritized in order to realign the incentives of academia with the practical needs of regulatory science, before it can realize its potential of contributing its valuable knowledge and resources to the field.
A Qualitative Study on HIV and Syphilis Testing Among MSM in the Pearl River Delta

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HIV is still a severe and pervasive issue on the global health stage with disproportionate impact among men who have sex with men (MSM). MSM are 19 times more likely to have HIV compared to the general population. In the context of the Pearl River Delta in China, the sexually-transmitted HIV epidemic has accelerated over the past five years along with the syphilis epidemic. The world’s largest syphilis epidemic is in China where in 2007 an average of one baby was born each hour with congenital syphilis. Because syphilis increases the risk of HIV acquisition and transmission and patients with either STI frequently attend the same STI clinics, there is compelling reason to assess both HIV and syphilis testing for MSM in the Pearl River Delta.

Although the twin epidemics of HIV and syphilis have common high risk groups and testing sites in the Pearl River Delta, widespread syphilis testing has been successful while sexually-transmitted HIV testing has been plagued by poor testing uptake. The spectrum of testing options for MSM range from conventional STI clinics to community-based organizations (CBOs). Examples of conventional STI clinics include centralized public hospitals and examples of CBOs include MSM-targeted non-governmental organizations.

We hypothesize that the low HIV testing acceptance among MSM is due to stigma that is unique to HIV, fear of disclosure and low perceived risk. Also, we hypothesize that the CBO model of testing would increase test uptake due to their MSM-targeted approach, anonymous testing, and STI education. To test these hypotheses, MSM attending CBOs in Guangzhou and Hong Kong were interviewed (n=35) on topics pertaining to HIV and syphilis testing, testing locations and stigma of HIV and MSM in China.

The audiotaped interviews are currently being transcribed and translated into English. The transcriptions and translations will be reviewed and themes across multiple interviews will be extracted by two independent researchers. The extraction of data will be undertaken in two phases. The first phase will identify major broad themes and then the second phase will delineate subtopics of importance with each of the broad themes.

With the data collected from this study, we hope to identify new avenues to increase uptake of both HIV and syphilis testing in the Pearl River Delta. Limitations for this study include sample selection bias due to recruitment of patients who already are utilizing CBOs as a testing site.
Implementation and Evaluation of the Impact of a Maternal Health Checklist in the Dominican Republic

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Despite the Dominican Republic’s (DR) classification by the World Health Organization (WHO) as a middle-income country, its maternal mortality rate (MMR) is persistently elevated – most recently 91.7 deaths per 100,000 live births versus 12-20 in the U.S. The most common cause of these deaths is hypertensive disorders of pregnancy, most notably, preeclampsia. We therefore undertook the implementation of a preeclampsia checklist and evaluation of its impact on the quality of maternal care. We hypothesized that use of this instrument would improve provider diagnosis and management of preeclampsia.

We conducted this work in the Hospital Maternidad Nuestra Señora de la Altagracia, the largest referral public maternity hospital in the DR. The implementation of the checklist involved presentations to the hospital leadership, physicians, residents, nurses, technicians, and students in the hospital. We also conducted interactive workshops with hospital personnel about the concept of a checklist, with its goals of reducing variation and errors, and the components of our preeclampsia checklist.

The checklist was incorporated into the protocols of the emergency and obstetrics departments. To assess the impact of the checklist on the quality of maternal care, women admitted to the hospital with a diagnosis of preeclampsia were followed via around-the-clock observation by a team of five observers for one month. Data were recorded for each patient during three phases: one hour after arrival in the emergency room (Phase 1), one half hour before delivery (Phase 2), and one hour after delivery (Phase 3). Care was evaluated for appropriate diagnosis of preeclampsia, use of magnesium sulfate, and monitoring of high-risk pregnancy patients.

Observational data were recorded for 91 patients; these data were analyzed with SAS statistical software and compared to baseline data collected from June to October 2011. Findings showed that, compared to baseline, the rate of performance of appropriate diagnostic tests for preeclampsia increased eleven-fold from 5% to 55% (p<0.0001) and the rate of confirmation of a suspected diagnosis of preeclampsia increased five-fold from 2.4% to 12.1% (p<0.0001). The rate of appropriate use of magnesium sulfate nearly tripled in Phase 1 (from 33.2% to 97%, p<0.0001) and increased by 62% in Phase 2 (from 33% to 53.6%, p=0.00148). No statistically significant changes were observed for the use of magnesium sulfate in Phase 3 or for the monitoring of high-risk pregnancy patients. Throughout the full cycle of care, the proportion of patients whose providers filled out the checklist ranged from 22.2% to 45.2%.

These results demonstrate that it is possible to make significant improvements in care processes through checklists. Our data also show that, despite a robust implementation process, the degree of adoption of the checklist by providers varied and that over-diagnosis of preeclampsia persisted during the study period. Further investigation into methods of incentivizing teams to adopt checklists and the outcomes of checklist adoption will be the focus of future studies. Limitations of this project include uncertain generalizability to other conditions and other institutions, challenges in attributing observed effects to the intervention, and low statistical power.
Almost half the world is at risk for malaria, and there are approximately 500 million cases and half a million deaths attributed to this disease each year. In humans, malaria is caused by five parasites of the genus *Plasmodium*, of which *P. falciparum* causes the vast majority of deaths and most cases of severe disease. Anti-parasitic therapy is often effective in treating malaria, but the continued evolution of drug resistance is a major problem. Drug resistance often emerges repeatedly from similar geographic locations; however, the reasons for this are unknown.

In this study, we applied whole genome sequencing to study the basic mutational properties of two *P. falciparum* isolates, one from Southeast Asia and known to rapidly evolve resistance to new drugs (the Accelerated Resistance to Multiple Drugs, or ARMD phenotype), and one from South America which lacks the ARMD phenotype. These lines were grown under normal culture conditions as well as in conditions of low-dose chloroquine pressure, for a period of up to 1.5 years. Using Illumina sequencing, we identified the mutations that occurred, characterized the dynamics of fixation and/or loss, compared the substitution rates for parasites from distinct geographic regions, and studied the evolutionary forces that drive the process of substitution in culture.

We observed a number of substitutions over the course of this experiment (~25), including both single nucleotide polymorphisms and insertions and deletions of varying size. We found an excess of substitutions in the line carrying the ARMD phenotype, suggesting that propensity to acquire drug resistance may be related to an increased baseline mutation rate. The dynamics of fixation for many of these variants closely mirrors what is expected under theoretical models of selection, suggesting that natural selection as well as genetic draft are powerful evolutionary forces acting during the asexual replication cycle, while the effects of genetic drift during these stages are weak. Overall, our data provide a view into the mutational landscape and basic evolutionary forces acting on *P. falciparum* during blood stage infection.
Towards a sustainable workforce: Increasing primary care graduates from research-oriented medical schools in the US

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Purpose: Historically, U.S. medical schools that identify as research institutions have produced fewer primary care graduates. With the growing national crisis in the primary care workforce, these schools should respond to meet the health-care needs of the nation. It is already known that specific elements of the medical school experience are correlated with more graduates choosing careers in primary care. This mixed-methods study investigates how these and additional factors operate within the context of research-intensive medical schools. We compare schools that have produced the highest percentages of primary care graduates (HP schools) with those that have produced the lowest (LP schools).

Methods: This is a set of mixed-methods case studies with cross case analysis using medical schools as cases. Primary data collection consists of both semi-structured key informant interviews with purposive sampling of primary care faculty, administrators and primary care student leaders from each medical school as well as focus groups with current primary care residents. Secondary data including the AMA masterfile, match data and previously published materials supplement primary data collection.

Results: We build on the theoretical framework developed by Bland et al to identify themes in the determinants of primary care specialty choice in the specific environment of research oriented medical schools. By triangulating the three data sources, utilizing qualitative and quantitative methods, a cross-case analysis was conducted to identify the factors that have the greatest success to influence student specialty choice at research institutions. We find that HP and LP schools differ in key areas such as quality, diversity and extent of clinical exposure to primary care and the degree to which the school facilitates interpersonal relationship building.

Conclusions: Previous literature is unable to address the changing environment of primary care practice and the specific environment of research-oriented medical schools. We make recommendations for increasing the number of primary care graduates from such institutions.
Ghrelin’s effect on T cell soluble RANKL production

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Periodontitis is a prevalent oral disease, affecting 17.2% of seniors over 65 years old worldwide. The bone resorption and inflammation seen in periodontitis are not caused by the bacteria itself present on tooth surfaces, but by an immune response to the bacteria. It is known that receptor activator of nuclear factor-kB (RANKL) plays an important role in osteoclastogenesis which facilitates bone resorption by binding to the RANK receptor present on pre-osteoclast surfaces and promotes osteoclast proliferation and differentiation. It was demonstrated that activated T cells are the cellular source of RANKL in the bone resorptive lesion of periodontitis. Activated T cells express membrane RANKL (mRANKL), which gets cleaved off into soluble RANKL (sRANKL). It is sRANKL that is the active form that promotes osteoclast maturation.

Ghrelin is a 28 amino acid acylated peptide hormone that is mainly released from the stomach. Although Ghrelin was originally thought to be a stimulator of food intake, recent evidence indicated a potential regulatory role of Ghrelin in the immune system. Ghrelin was in fact detected in human saliva and is produced by T cells to down-regulate concentration of proinflammatory cytokines. Since T cells also produce RANKL, a pro-osteoclastic cytokine, it is then natural to ask if Ghrelin has any effect on RANKL production. We hypothesize that Ghrelin decrease sRANKL production because it downregulates other pro-inflammatory cytokines.

We wanted to find if Ghrelin inhibits sRANKL in a dose dependent manner. We isolated T cells from harvested mouse spleens and stimulated with immobilized CD3/CD28 antibody. Varying concentrations of Ghrelin and MK667 (0nM, 1nM, 100nM, 1uM and 10uM) were added and incubated for 24 hours. After the allowed time period, we use enzyme-linked immuno sorbent assay (ELISA) to detect sRANKL levels in supernatant. We expected to see a dose-dependent decrease in sRANKL levels with increasing Ghrelin concentration.

What was most surprising was that Ghrelin did not inhibit sRANKL production as we originally hypothesized. Instead, there was a statistically significant, dose dependent increase (p<0.05). This is the first reported evidence of Ghrelin’s effect on sRANKL levels. Further experiments need to be performed to confirm these findings and elucidate purpose of RANKL upregulation.
Medicaid prescription limits: policy trends and comparative impact on utilization

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Medicaid programs face growing pressure to control spending. Despite evidence of clinical harms, states continue to impose policies limiting the number of reimbursable prescriptions (caps). We evaluated the recent use of cap policies by state Medicaid programs and examined the impact of cap policy implementation on prescription medication use and spending.

We collected data on Medicaid cap policies from 2001 to 2010. These were classified as applying to all medications (overall caps) or only to branded medications (brand caps). Using state-level, aggregate prescription data for scripts and spending, we developed interrupted time-series analyses to evaluate the impact of cap implementation on prescription medication use, including terms to estimate the immediate (level) change and ongoing change over time (slope).

We classified essential medications that prevent significant morbidity or mortality as preventive or as providing symptomatic benefit. We examined the number and costs of prescriptions for the following medications. Overall caps: all essential medications, preventive essential medications, and symptomatic essential medications. Brand caps: all branded medications, branded and generic medications among classes with available generic replacements.

The number of states with caps increased from 12 in 2001 to 20 in 2010. Overall cap implementation (n=3) led to an annual slope decrease of 0.52% (p<0.001) in the proportion of essential scripts but no change in cost. For preventive essential medications, overall cap implementation led to a 1.12% (p=0.001) annual slope decrease in scripts (246,000 prescriptions annually), and a 1.20% (p=0.001) annual slope decrease in spending (-$12.2 million annually), but no decrease in symptomatic essential medication use. Brand cap implementation (n=6) led to a 2.29% (p=0.16) level decrease in branded scripts and 1.26% (p=0.025) level decrease in spending. For medication classes with generic replacements, the level decrease in branded scripts (0.74%, p=0.003) approximately equaled the level increase in generics (0.79%, p=0.009), with estimated savings of $17.4 million annually.

An increasing number of states are using caps, with mixed results; by 2010, 58% of Medicaid enrollees lived in states with caps. Overall caps decreased the use of preventive but not symptomatic essential medications, suggesting that patients assign higher priority to agents providing symptomatic benefit when faced with reimbursement limits. For medication classes with generic replacements, brand caps shifted usage from branded drugs to generics without decreased use, resulting in considerable savings. Future research should analyze the patient-level impact of these policies to measure the clinical outcomes associated with these changes.
Laryngeal cancer, one of the most common head and neck cancers, will be diagnosed in over 12,000 people in the US this year. Although this cancer is largely curable, those with advanced or recurrent laryngeal cancer may require the complete removal of their larynx—laryngectomy. This procedure alters respiration, deglutition, taste and smell. Devastating to patients, however, is loss of voice. Several procedures have been developed to restore voice to these patients, the most successful of which is tracheoesophageal puncture (TEP). In this procedure, a tract between the trachea and esophagus is created that can accommodate a one-way prosthesis for voice rehabilitation. Classically, the TEP is performed after the patient has recovered from total laryngectomy. However, performing the TEP at the time of laryngectomy eliminates the need for multiple surgeries, and thus has become the favorable option at the Massachusetts Eye and Ear Infirmary (MEEI).

In order to determine whether TEP at the time of laryngectomy (primary TEP) is associated with equivalent or better outcomes as compared with TEP at a subsequent date (secondary TEP), we have undertaken to catalogue the histories of all patients at MEEI who underwent TEP from January 1, 2000 to July 11, 2011. In an effort to enable future studies that assess the outcomes of patients as they relate to other elements in the patient history, we have widened the scope of our database to include many details of the patient histories. These include, but are not limited to, past medical history, cancer staging, timing of prosthesis placement, and complications of the procedure. We are also collecting patient demographics in this database. These details will help to assess the generalizability of its results.

Although data collection is still underway and I have not yet reached conclusions about preferable surgical interventions, I have gained interesting insights into the process of performing a chart review. My experience has shown that the growing number of hurdles required to gain approval for such a project can at times prove to be quite challenging. It is our hope that results from this chart review study and future studies utilizing our database will improve the overall success in voice restoration and quality of life for TEP patients.
Content Analysis of Dentist-directed Advertisements in Dental Journals

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Dentist-targeted advertisements may influence clinical judgments of dentists and affect the health of dental patients. Such advertisements are found in the majority of printed paid-subscription and controlled-circulation journals in dentistry. Since dental devices are considered to be medical devices by the FDA, advertisements of dental devices should adhere to the FDA’s guidelines for truthful advertising.

Based on previous studies on US-based biomedical journals, we hypothesized that approximately 50% of advertisements are non-adherent to the FDA’s guidelines. We also hypothesized that the type of journal in which they are published to be an effect modifier. To test these hypotheses, 31 journal issues from 8 US-based printed dental journals ranging from December 2011 to July 2012 were sampled based on their availability in the Countway library of Medicine. Advertisement-only pages were scanned and total page number was recorded for each journal issue.

Advertisements of products that were considered medical devices were categorized by device type and/or dental specialty: adhesives, endodontic, general instrument, grafting, imaging, implant, impression, orthodontic, patient hygiene, patient safety, pharmaceutical, prophylaxis, prosthetic, restorative, and whitening. Content analysis for adherence to the FDA’s guidelines regarding claim of benefit, information on risks, use of headline, and use of graphics were done by two reviewers.

In our study sample, paid-subscription issues (n=14) had a higher percentage of advertisement-only pages than controlled-circulation issues (n=17) (mean±SD, 40.3±10.6 vs. 14.2±5.7; p<0.05). Preliminary analysis of adherence showed a significant number of non-adherent advertisements from both journal types due to lack of peer-reviewed evidence, lack of information on risks, and/or misleading headlines. However, further analysis needs to be completed to determine and compare non-adherence rates by journal type and advertisement category, as well as to calculate inter-rater reliability.

Over-sampling was a limitation of this study in order to obtain a more balanced number of issues in each journal type, given the availability of printed journals. Since the FDA’s guidelines presumably were designed mainly for pharmaceutical agents, certain criteria may not be suitable for dental devices. Nevertheless, this study highlights the potential for advertisements to negatively influence clinical judgments of dentists.
The Impact of California Emergency Department Closures on Inpatient Mortality

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In recent years, hospital emergency departments (EDs) in the United States have come under unprecedented strain. Between 1996 and 2009, the annual number of ED visits in the US increased by 51% while the number of EDs nationwide decreased by 6%, leading to increased ED crowding and wait times and overextension of ED staff. Studies have also shown that communities with more Medicaid, low-income, and racial and ethnic minority patients are at higher risk of having their EDs close, a trend that may act to widen disparities in access to health care. These challenges were so significant as to prompt the Institute of Medicine to conclude in a 2007 report that US EDs are “at the breaking point.”

While recent studies have shown that ED closures are associated with poorer outcomes for patients with acute myocardial infarction and other time-sensitive conditions, none has investigated the impact of closures on inpatient mortality for a general population. Furthermore, these past studies have generally used ED crowding or change in travel distance to the nearest ED as surrogates for ED closures, rather than investigating the effects of closures directly.

To improve our understanding of these effects, we examined the association between ED closures in California in 1999-2010 and the inpatient mortality rate of patients hospitalized near those closures. We identified all instances of ED closure during the study period using the California Office of Statewide Health Planning and Development (OSHPD) Hospital Annual Utilization Data files, supplemented and verified with phone calls to hospital administrators and public health authorities. We defined relevant ED closures as those occurring within the patient’s Hospital Service Area (HSA), as defined by the Dartmouth Atlas Project, and we obtained patient-level mortality data from the California OSHPD Patient Discharge Data files.

In our analysis, 25.1% of admissions studied experienced an ED closure in their HSA and 74.9% experienced no closure. Patients exposed to ED closure experienced a higher odds of inpatient mortality than those not exposed to closure (adjusted odds ratio, 1.05; 95% confidence interval [CI], 1.02-1.09). In our sensitivity analysis classifying admissions as “exposed” only when they occurred within 2 years of an ED closure in their HSA, the increased mortality for patients exposed to closure persisted (adjusted odds ratio, 1.04; 95% CI, 1.02-1.07). These findings may have implications for policy decisions regarding the organization, regulation, and financing of emergency care.
Diabetes Peer Support Program: Development of a Primary Care Telephone-Based Program for Patients with Poorly Controlled Diabetes

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In Healthcare Associates, the academic primary care practice at Beth Israel Deaconess Medical Center, over 500 patients have HbA1c >9. Thus, there is great need to help patients improve their disease status. Peer mentoring programs has demonstrated significant improvement in diabetes outcomes. Based on the success and low-resource demand of the peer-mentoring model, we wished to develop and test a telephone-based peer support program for patients with type 2 diabetes.

Physician-referred patients with HbA1C <8 were recruited to be patient mentors. Patients provided telephone feedback on mentor training, incentives, partner relationship and barriers. Mentors underwent a 3-hour training and were instructed to call mentee weekly to discuss goal setting and provide support. Patient mentors were then paired with patients with poorly controlled diabetes to provide telephone support for 3-6 months. Measures of success included change in HbA1c, diabetes self-efficacy, diabetes self-care, physical activity and healthy eating frequency, diabetes literacy.

Feedback from 10 patients highlighted the importance of weekly peer contact, similar medication requirements and concluded that incentives were not necessary. 12 mentors and 9 mentees have enrolled in the program. 75% of mentors and 90% of mentees were female. Mean HbA1C of mentors and mentees were 6.87% and 8.37% respectively. Mentors were more likely to be older (71.4% of mentors versus 0% of mentees >60yo) and of white race/ethnicity compared to the mentees (71.4% versus 33.3%). Mentors were also more likely to check their blood glucose, take their medications as instructed, engage in more light or moderate physical activity (mean of 10.9 hrs versus 3.4 hrs/week), and have higher diabetes literacy scores (mean of 62.2% versus 41.1%) and self-efficacy (mean of 8.21 versus 4.94 on 10-point scale). Mentor diabetes literacy did not change significantly after the training session (72.5% versus 77.5%).

Marginal improvement in mentor diabetes literacy post-training may be due to existing high baseline diabetes literacy. The gap in nutrition, physical activity, and self-efficacy between mentors and mentees suggests that mentors have great opportunity to assist with mentees in these areas. The main challenge that we continue to address is increasing mentee recruitment, a challenge that may be related to working with a patient population with many barriers to care. Foreseeable limitations to this study include patient participation in other diabetes programs and generalizability beyond the Beth Israel patient population.
Reflective Writing as a Pedagogical Tool
to Enhance Physician Empathic Communication

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Skilled empathic communication by physicians correlates with improved patient outcomes, higher family satisfaction, and reduced adverse family bereavement outcomes. Despite these benefits, erosion of empathy occurs during training, notably during the third year of medical school and throughout residency. Reflective writing has been used in medical schools as a tool to promote student professionalism and empathic communication skills. However, little is known about whether such interventions could be sustained among practicing physicians. The study aims to test whether adding a brief reflective writing component to an existing communication course will be associated with a greater self-reported and observed empathic communication.

This project is woven into a required weekly communication course for residents during their rotation in the Intensive Care Unit at a tertiary care hospital. Methods include faculty-led interactive discussions, role play with volunteers, and simulation with feedback. Brief, 2-3 minute reflective writing exercises are administered prior to the role play of the following scenarios: leading an initial meeting with the family of a recently admitted ICU patient; and a follow-up meeting to discuss goals of care for the patient. Residents in the intervention groups are asked to imagine themselves in the family member’s place and describe what they might be thinking and feeling in such a situation; the comparison groups will be asked to focus on medical aspects of the case only. Residents are also interviewed at the end of the course to explore their experience of the reflective writing practice and of the course overall. Audio-recorded interviews are transcribed and analyzed using qualitative methods of content analysis.

Preliminary results for the qualitative interviews are as follows: Nine residents in the intervention group have completed interviews; all described the reflective exercise as helpful, because of the following themes: the exercise brought family’s experience to the forefront; shifted attention from their own agenda (e.g., needing a decision) to considering the family’s concerns; encouraged awareness of their use of language, especially avoidance of medical jargon; counteracted the impact of time pressures to consider the impact of events on the family; and helped resident to formulate a clear agenda before meeting with family.

Conducting a brief reflective writing session is feasible and may enhance residents’ ability to understand the perspective and needs of family members. Next steps will be to assess whether reflection on the family experience results in greater observed empathic communication compared with reflection on medical aspects of care alone.
Optimizing the Decellularized Matrix for Tracheal Regeneration

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Current clinical treatment of benign and malignant tracheal disorders involves surgical resection and end-to-end anastomosis when the length of the diseased segment is less than half the tracheal length in adults or one-third the tracheal length in children. Conventional allotransplantation of a donor tracheal segment is technically feasible but requires lifelong immunosuppression and results in allograft necrosis, infection, and eventual death due to improper revascularization and continual contact with the external environment. The use of autologous allografts and artificial prostheses has also been met with limited success. A more promising approach is the use of decellularized tissues to obtain acellular, biologic scaffolds upon which cells of interest can be seeded. In this study, we implemented a novel decellularization method using a constant transmural pressure gradient to optimize the decellularized matrix for tracheal regeneration. We decellularized porcine and human tracheas by perfusing the inner lumen with an SDS detergent solution at a constant pressure of 150 mmHg. The resulting decellularized matrices were assessed qualitatively and quantitatively through histology, matrix characterization assays, and biomechanical measurements. Histological examination of the decellularized tracheal matrices revealed complete decellularization of the epithelium, mucosa, and submucosal glands and near-complete (90%) decellularization of the cartilaginous rings. The majority of the lacunae within the cartilaginous rings were completely void of any cellular components, and the remaining lacunae only had nuclear debris with no intact chondrocytes present. Immunofluorescent staining for major histocompatibility complex class I (MHC-I) and collagen type IV demonstrated low immunogenicity of the decellularized tracheas and maintenance of the basement membrane, respectively. Quantitative measurements of various matrix components showed a significant decrease in DNA in the decellularized samples but preservation of collagen, glycosaminoglycans (GAGs), and elastin. Biomechanical measurements of the decellularized tracheal matrices revealed a decrease in tensile strength of the cartilaginous rings and an overall increase in compliance. This study demonstrates that a constant transmural pressure within physiologic limits allows for a much more complete decellularization of tracheas with optimal preservation of the extracellular matrix as compared to previous studies. However, the heterogeneity in the cartilaginous thickness of the tracheal samples may require trachea-specific optimization in terms of perfusion pressure and cycle length in order to maximize both decellularization and matrix preservation. Moving forward, we have developed a biomimetic perfusion system to reseed these decellularized tracheal matrices with primary human tracheal epithelial cells and human mesenchymal stem cells (hMSCs) and generate a clinically transplantable tracheal graft.
Novel HSP90 and EGFR inhibitors as potential therapeutics for melanoma

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Melanoma is the fifth and sixth most common cancer in men and women, respectively, in the United States. Once metastatic, melanoma has a dismal median survival of around 6 months and is resistant to conventional therapies. Therefore, there is a great need for novel therapies in metastatic melanoma.

As a molecular chaperone that stabilizes many signaling proteins, heat shock protein 90 (HSP90) has an important role in the regulation of signaling, proliferation, and cell survival. Inhibition of HSP90 has been shown to lead to the degradation of signaling molecules responsible for malignant growth, making it an attractive target in cancer therapy. Similarly, EGFR signaling is important in tumor growth and its inhibition has been shown to be effective in treating various solid tumors. In melanoma, increasing expression of EGFR has been detected and is associated with progression and metastasis. Therefore, we hypothesized that HSP90 and EGFR inhibition could be a potentially effective therapy in metastatic melanoma.

To test this hypothesis we treated melanoma cell lines with either the potent ATP competitive inhibitor of HSP90, Ganetespib, or a novel EGFR inhibitor (EGFRi). We found that both Ganetespib and EGFRi inhibited growth and induced apoptosis in a panel of melanoma cell lines with various genetic backgrounds. Importantly, Ganetespib and EGFRi were still effective in BRAF mutated melanoma cells that had acquired resistance to B-RAF inhibition. Molecular studies showed that cell cycle arrest induced by Ganetespib was associated with an increased expression of cyclin-dependent kinase inhibitor (CDKI) p21\(^{\text{Cip1}}\) and p27\(^{\text{Kip1}}\) and decreased expression of cyclin E, cyclin-dependent kinases 1 and 4. Ganetespib downregulated the expression and/or activation of multiple growth signal transducing molecules critical for cell growth and survival in melanoma cells. EGFRi induced a potent G2 cell cycle arrest with corresponding upregulation of p21. EGFRi also reduced the expression of prosurvival genes Bcl-2 and Mcl-1. These findings provide insights into the molecular mechanisms by which Ganetespib and EGFRi induced growth inhibition and apoptosis in melanoma cells.

In summary, we have shown in vitro anti-melanoma activity of Ganetespib and EGFRi at low nM concentrations. Our findings suggest that Ganetespib and EGFRi could potentially be effective therapies for melanoma with various genetic mutations and acquired resistance to B-RAF inhibition.
Partners in Health (PIH) recently wrote a fourteen-chapter Program Management Guide (PMG) designed to aid organizations and individuals in the establishment of healthcare initiatives in developing countries. The utility of the PMG outside the infrastructure and resources of PIH was assessed using in depth interviews and questionnaires. The aims of this study were to: 1) Systematically gather feedback from in-field experts regarding the perceived need and utility of the PMG guide, 2) Evaluate the PMG's content, format, organization, and suitability for diverse target audiences by examining three out of the fourteen chapters, and 3) Establish possible strategies for adaptation, dissemination and future evaluations of the PMG in other settings. Four leading members of a new NGO named Primary Health Care International (PHCI), and four program managers in and from Harare, Zimbabwe, were chosen to assess the perspectives of two distinct target audiences. The in-depth interviews were approximately forty-five minutes long. The twenty-four question surveys were anonymous and not linked with the interviews in any way. All interviews have been transcribed, but analysis of the transcripts to identify the prevalent themes is ongoing. Preliminary results from the transcriptions reveal that most participants felt that the PMG needed more utilitarian features such as checklists, and less lengthy narratives. There are widely varying opinions on the PMG depending on the type and stage of the NGO or program in which the interviewee is involved. The data gathered from the interviews and surveys will help improve the efficacy, appropriateness and acceptability of the PMG. It will also help to describe the contexts in which the PMG can be utilized. The potential broader use of the PMG can allow for more collaborative sharing of best practices within the global health community, and more efficient use of global health funding.
A Qualitative Study on Patient Perceptions Toward mHealth Technology Among High Risk, Chronic Disease Patients

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For the past 15 years, the Prevention and Access to Care and Treatment (PACT) Project based in Boston has actively developed a Community Health Worker model for care of chronically ill, high risk patients. By integrating community health workers (CHWs) into care delivery, PACT aims to improve the health outcomes of the neediest and most high risk/high cost patients. As part of the expansion of PACTs work, they plan on implementing Mobile Health technology to be used by patients in order to support care management and patient-self management. PACT will use this mobile health technology (mHealth) for targeted interventions such as medication and appointment reminders, and the collection of patient reported outcomes (PRO) measures.

In order to inform mobile health design, we had focus groups with the target population to test the hypothesis that the patients will be receptive towards using mHealth technology as a tool for interventions and PRO collection. Key domains of interest are learning about the perceived feasibility and accessibility of mHealth technology, potential uses of mHealth tech and exploring perceived facilitators and challenges to mHealth uptake by the representative patient sample. Additionally, we examined potential effects of age on technology literacy and accessibility of mHealth technology. We hypothesized that older populations may have less familiarity with mobile based technology and hence there may be a difference in attitudes towards mHealth technology.

The study consisted of 4 focus groups with the target population. All recruited patients were adult patients (>21 age), English Speaking, co-Morbid (2 or more chronic health conditions, and low SES as determined by hospital staff (Medicaid and/or Dual Eligible). The focus groups were stratified by age >55 y.o (n=8 and 5) and <55 y.o. (n=7 and 7). All focus groups were audio recorded and a full transcript was made of each session.

The transcripts from the FGs will be analyzed in order to assess patient perceptions on the use of mHealth technology for their health management. The written transcripts will be uploaded and analyzed for trends and themes using the qualitative research software. The qualitative analysis based on grounded theory methodology. All of the transcripts will be divided into quotes which are coded for important key points. Once all the data is coded, the quotes can be organized into concepts or themes. From these themes we will generate categories which we will analyze for content.
Complementary Efforts to Reinforce the Implementation of Oral Cholera Vaccine in Rural Haiti

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In October 2010, the first cases of cholera were documented in Haiti. To date, it has affected 590,856 individuals and led to the death of 7,558. Cholera is on its way to becoming endemic in Haiti and will likely be a significant cause of morbidity and mortality for years to come.

Cholera is a largely preventable water-borne disease, and the implementation of clean water solutions and vaccination is crucial in curtailing its spread. In April of 2012, Zanmi Lasante (ZL) – the Haitian sister organization of Partners in Health (PIH) – and GHESKIO began the first oral cholera vaccine rollout on the island. Two months later, nearly 100,000 Haitians had been successfully vaccinated; over 90% of individuals who received the first dose of a two-dose vaccine came back for their second dose, far surpassing prior estimates. Investigations are underway to establish the field efficacy of the vaccine, and to implement point-of-use clean water solutions as a complement to vaccination.

This project first sought to quantify the number of cholera cases presenting to the cholera treatment unit (CTU) in Saint Marc, Haiti, where PIH/ZL implemented the rural branch of the vaccination pilot. We documented the number of cases presenting from the beginning of the epidemic up to July 2012, and quantified the number of cases originating from regions that received cholera vaccine. The overall pattern of case incidence rates aligned with national trends, and overall is much lower now than at the beginning of the outbreak. Second, we sought to assess access to clean water in regions receiving vaccine. Community water sources were mapped using GIS technology and tested for fecal contamination. Major sources of water included the Artibonite River, unprotected wells, water pumps, and water treatment units. Overall, access to clean water was poor and many use the river as their main water source. Water from the river and unprotected wells was highly contaminated. While some water pumps were uncontaminated, others showed some contamination due to improper maintenance. Water from treatment units was mostly uncontaminated; however, few people use these units, perhaps owing to cost.

Case incidence data give us a baseline against which we can compare post-vaccine incidence rates, and will aid in the planning of subsequent vaccine efficacy studies. These data also provide a geographical and qualitative appreciation of water access in the region, and will help us better implement clean water solutions while developing a complementary cholera prevention program.
The Social and Cultural Grounding of Body Image in Central Ghana

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Traditionally, Ghanaian culture has preferred women of larger build, with this body type being indicative of affluence and social standing. Within the past few decades, Ghana has experienced increasing urbanization, transitioning nutritional habits, ever more widespread media exposure and expanding knowledge about personal health and well-being (Agyei-Mensah and de-Graft Aikins 2010). These factors all have the potential to influence body image perspectives and lifestyle choices. The purpose of this project was to assess ideal body image perspectives among adult men and women in a regional urban center in Ghana in order to identify which social and culture influences are most pervasive within the community, to isolate which influences are perceived to have the largest impact on ideal body image, and to understand the correlates and effects of different body image perspectives. 400 Ghanaian men and women were selected at random from among the patient population of the Central Regional Hospital and the Abura Dunkwa District Hospital (Central Region) and asked to complete a 15 minute verbal survey that assessed their opinion on ideal body image, measured their exposure to a number of cultural influences and elicited a self-report of the impact of various influences on ideal body image. Participants were also weighed and had their height, waist and hips measured in order to provide BMI and waist/hip ratio data. The results showed notably high levels of overweight and obesity, particularly among women. Participants also reported high levels of exposure to all forms of media measured, with television rated as the most influential form of media. Notably, increasing television exposure correlated with increased body image dissatisfaction. Among social influences, participants rated spouse/partner as having the most influence on their body image, and reporting of a strong influence from either spouse/partner or friends was associated with greater body dissatisfaction. Overall, our results suggest that a variety of competing influences are at work on the body size and body image of Ghanaians, and these are made manifest in a high rate of body image dissatisfaction.
A prospective study of circulating macrophage inhibitory cytokine-1 (MIC-1) levels and risk of colorectal cancer

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Chronic inflammation may play a role in colorectal carcinogenesis. We examined the association between the novel plasma biomarker macrophage inhibitory cytokine 1 (MIC-1) and the risk of colorectal cancer in a nested case-control study from the Health Professionals Follow-Up Study (HPFS) as well as from the Nurses’ Health Study (NHS).

We conducted a prospective, nested case-control study of cases of incident colorectal cancer through 2008 follow-up matched to up to 2 controls on age and date of blood draw. MIC-1 levels were measured using an ELISA. Associations between quintiles of MIC-1 and colorectal cancer risk were calculated using unconditional logistic regressions (NHS/HPFS). We also assessed the relationship between MIC-1 levels and PTGS-2 (COX-2) enzyme status in tumor tissue samples. Analyses were adjusted for matching factors and for known or suspected risk factors for colorectal cancer.

Median plasma MIC-1 concentrations among colorectal cases approached significance relative to MIC-1 levels in controls (0.0881). In pooled analyses of NHS and HPFS, compared to those in the lowest quartile of plasma MIC-1 (Q1), men and women in the highest quintile (Q5) had a multivariate RR for CRC of 1.95 (95% CI, 1.289 - 2.951, p for linear trend = 0.0022). In exploratory analyses of cases for whom PTGS-2 status was assayed, it appeared that the association of MIC-1 with colorectal cancer risk was stronger for PTGS-2 positive cancers than PTGS-2 negative cancers.

Our results support an association between higher levels of circulating MIC-1 and colorectal cancer. The association appeared to be stronger for PTGS-2 positive cancers.
Cost effectiveness of providing surgical care at a district level hospital in rural Rwanda

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**Background:** In a community dominated by communicable diseases, the provision of surgical services in the developing country setting has been viewed as too expensive by public health experts and international aid funders. Our study aims to show that providing surgical services as the district level can be a cost-effective public health endeavor.

**Setting:** Rwinkwavu Hospital is one of 45 district hospitals in Rwanda. It serves approximately 160,000 people, half of which live on less than USD$1 per day. The 110-bed hospital employs 10-12 generalist physicians who perform basic surgical services, including emergency obstetric care.

**Methods:** We recorded the direct material and human resource costs and estimated a fraction of indirect overhead costs attributable to providing surgical services at Rwinkwavu. We calculated the disability adjusted life years (DALYs) averted through the provision of surgical care based on estimations of threat to life and the efficacy of treatment for all patients treated in 2009.

**Results:** Total costs for providing surgical services at Rwinkwavu in 2009 were calculated to be USD$792,300. Recurring overhead (including maintenance, fuel and administration) accounted for 42.6% of costs, a proportion of fixed equipment and instruments was 32.8%, consumables and medications 31.3%, local staff 12.0%, and expatriate physicians were 7.4%. Total DALYs averted by surgical care in 2009 was estimated between 5457 DALYS(3,1,0.4) and 9477 DALYS(0,0,0). The majority of DALYs averted (60-66%) were due to risk to unborn infants during a complication of pregnancy requiring a caesarian delivery. Cost effectiveness was calculated to be USD$83-145 per DALY averted.

**Conclusions:** The cost effectiveness of providing surgical services at the district hospital level in rural Rwanda compares favorably with other commonly supported global health initiatives such as measles vaccination (USD$5 per DALY) or antiretroviral therapy for HIV (USD$300 per DALY) and should therefore be included as a public health priority.
Clinical Pathway Development For Acute Axial Low Back Pain

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As the US healthcare system continues to shift away from volume-based to value-based care, health systems must focus on improving quality and outcomes while reducing cost. Clinical pathways founded on evidence-based practice are effective tools hospitals can utilize to streamline delivery of care to reduce unnecessary variation and improve the value of care delivered. Once the pathways are built, they can be utilized alone to help improve care, or can be used as tools to integrate bundled payment reimbursement schemes.

Acute axial adult low back pain was selected for clinical pathway design. To ensure diverse perspective in pathway development, physicians from multiple disciplines, physical therapists, and administrators were included in pathway development. Recommendations and definitions were obtained from primary peer-reviewed literature and brought to consensus by content experts within the group.

The clinical pathway defines terms and conditions rigorously to remove ambiguity. It first lists warning signs to rule out certain conditions, such as cauda equine syndrome, infection, etc., that require emergent treatment or immediate consultation. The pathway incorporates guidance for patient education and branch point opportunities to incorporate patient preference into the treatment decision tree. Best practices are provided for home exercise programs and physical therapy regimens, as well as important mental health screenings that should be performed during evaluation. Additionally, recommendations for evidence-based medication and radiological imaging use, as well as follow up and referral to specialty care, are provided to inform clinical decisions.

The clinical pathway has the potential to improve the quality of care delivered to patients while at the same time reducing unnecessary testing and interventions that occur as a result of variation between providers. It is essential that these pathways be implemented and their adherence and variation studied. Implementation involves close integration with electronic medical records and decision support. Ultimately, building consensus-based clinical pathways for many disease states will help providers and hospitals deliver higher quality care more efficiently, and integrating them into quality-focused bundled payment methods will help hospitals deliver higher value care.
Evaluating the use of village health workers for household health monitoring in Neno, Malawi

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Malawi is a small, land-locked country in southern Africa, and is one of the poorest countries in the world. Partners in Health’s Malawi site, Abwenzi Pa Za Umoyo (APZU) has partnered with the Ministry of Health since 2007 to strengthen the health care system and community health programs in Neno, a rural district in southern Malawi. The hub of the community health programs is a village health worker (VHW) program serving the 125,000 residents of the district. APZU has implemented a household chart, which VHWs associated with 3 of the 13 health centers use to document disease screening, services delivered, and referrals to facilities for care.

The overall goals of this project were: 1) to evaluate the effectiveness of the VHW household chart in increasing active case finding and referral to care; 2) to examine through qualitative interviews whether improvements in data management have increased utilization of the VHW-generated household chart data. The quantitative portion of this project relied on healthcare utilization data routinely collected at health facilities in Malawi. Due to challenges with health facility data quality, differences between health center catchment areas, and other variables contributing to potential secular trends in healthcare utilization, I was unable to report robust results from the quantitative portion of the project. However, identifying the issues with facility data quality led to new collaboration between APZU and Ministry of Health employees to improve data quality. In the qualitative interviews, both APZU and Ministry of Health stakeholders agreed that the VHW-generated data helped them identify important unaddressed health issues such as areas with low antenatal care usage, low immunization coverage, or high incidence of malnutrition. In some cases, these data enabled timely interventions, while in other cases both APZU and the Ministry of Health struggled to mobilize the resources to address a need identified by the VHW data. Ministry of Health employees also suggested that the presentation of the data collected as well as collaboration with APZU staff members could be improved.

In conclusion, the VHW household chart has the potential to improve referral to and utilization of rural health services. Work to address identified gaps in health facility data are planned, which may help future measurement of the impact of the household chart. Increased collaboration between APZU and the Ministry of Health might also improve their ability to respond quickly to needs identified by the household chart.
Development of a Quality Improvement Program for the Management of Pediatric Dehydration in St. Marc, Haiti

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Barriers to providing quality medical care in hospitals and clinics in developing countries include limited human and material resources, weak systems, and competing demands for available service capacity. The goal of improving quality is also challenged by limited programs for evaluating and improving services.

Hôpital Saint Nicolas (HSN) is the primary hospital for the people of St. Marc, Haiti and the 1.5 million people in the Artibonite region. Their pediatric department admits about 190 patients per month and is usually staffed by two doctors and five nurses. Dehydrated patients between the ages of 0 and 15 years old account for about one third of pediatric admissions, and the typical treatment, regardless of severity, is intravenous fluids and antibiotics rather than oral rehydration solution (ORS), which is effective for those with less severe dehydration. Improper treatment results in longer length of stay and requires resources that could be better utilized by more severely ill patients. We sought to improve the management of dehydration by implementing a checklist for diagnosing dehydration and an oral rehydration station for treating dehydration cases in the pediatric ward.

In order to understand where there was area for improvement in the quality of care for dehydration, we initially performed a six-month chart review to assess reasons for admission, length of stay, and type of treatment prescribed. We found that no standard operating procedures existed for rehydration so we used the World Health Organization’s guidelines on pediatric rehydration to create an admissions checklist and protocol poster for doctors and nurses, and we trained the nurses on the use of these standardized protocols. Our goal was to ensure that all dehydrated patients were properly classified as mild, moderate, or severe and then received treatment appropriate to their severity. We also established a physical rehydration station in one corner of the pediatric ward to facilitate the use of ORS for both less severe inpatients and for outpatients to prevent the need for admission. The rehydration station provides potable water, ORS packets, education for parents and caretakers, and monitoring of acute dehydration in a setting that best utilizes the limited number of healthcare providers.

In the coming months, ongoing data collection is being performed to evaluate if the implementation of this dehydration treatment program can reduce the number of dehydration admissions and unnecessary use of IVs and antibiotics.
Influence of metabolic regulation on primary cell proliferation and differentiation

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Cancer cells exhibit unique metabolic properties to support biosynthesis for rapid proliferation. The regulatory properties associated with the M2 splice isoform of pyruvate kinase (PKM2) appears to be important for anabolic metabolism in proliferating cells. Pyruvate kinase catalyzes the last step of glycolysis, generating pyruvate from phosphoenolpyruvate. PKM2 is unique among pyruvate kinase isofroms in that its enzymatic activity is regulated by multiple factors, including growth signaling. In contrast, the M1 splice isoform (PKM1) has high constitutive activity and is expressed in tissues with high ATP requirements. Paradoxically, it is the ability to decrease PKM2 activity that is linked with both anabolic metabolism and cell proliferation arguing that pyruvate kinase can influence the metabolic program in cells toward an anabolic or catabolic state.

We hypothesized that the low-activity PKM2 isoform allows for a buildup of upstream glycolytic intermediates that serve as a source of biomass for rapid proliferation. In addition, we hypothesized that PKM2 expression is necessary for the maintenance of an undifferentiated cell state.

To test these hypotheses, we cultured primary cells from mice with conditional PKM2 alleles. Myoblasts (skeletal muscle precursors) and mouse embryonic fibroblasts (MEFs) both express PKM2, but when the PKM2-specific exon is deleted by expression of Cre recombinase, these cells express PKM1 and stop proliferating. Use of small molecule PKM2 activators or deletion of one PKM2 allele leading to co-expression of both PKM1 and PKM2 in the same cells also arrested proliferation, suggesting that the high pyruvate kinase activity associated with PKM1 is sufficient to inhibit cell proliferation.

Further characterization of these primary cells showed that loss of PKM2 and subsequent PKM1 expression in MEFs led to significantly reduced flux to the nucleotide and serine biosynthesis pathways, which branch off from glycolysis upstream of pyruvate kinase. DNA content analysis showed that PKM1-expressing MEFs are arrested in the S- and G2-phases of the cell cycle, and one possibility is that a paucity of nucleotide precursors contributed to this arrest.

PKM2 deletion leading to PKM1 expression in myoblasts also inhibited proliferation, but did not promote differentiation in nutrient rich conditions. However, in poor-nutrient conditions, a switch from PKM2 to PKM1 did promote myoblast differentiation into myotubes, suggesting that altered metabolism may serve as a differentiation signal. Taken together, these data raise the possibility that PKM2 expression is selected for in proliferating tissues (including cancer) because it allows for anabolic metabolism and supports a less differentiated state, while PKM1 antagonizes those processes.
Is Food Allergy an Infectious Disease? Surveying the Microbiome in Food Allergy

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Food allergy has become a major public health concern whose prevalence has grown dramatically in just the past decade. The sudden rise of prevalence in food allergy and other atopic diseases such as asthma suggests a role of changing environmental exposure in early childhood when these diseases typically present. Research suggests that the composition of the intestinal microbiota in infants is essential to the development of immune tolerance and is sensitive to numerous environmental exposures. Therefore, we hypothesize that the increase in prevalence is related to changes in the microbiota present in the infant intestinal tract.

To test this hypothesis, 30 well characterized food allergic children and 30 age-matched controls without food allergy are being recruited from the allergy immunology clinics at Children’s Hospital. Study subjects are infants with a documented history of food allergy. Clinical history is being collected, along with routine laboratory evaluation. Parents are given a kit for collecting stool samples at home when the infant is 12 months of age, which will be sent to collaborators at the Broad Institute for DNA amplification and sequencing to determine bacterial species. The primary endpoint of this study is to determine differences in overall diversity between the two groups, using appropriate statistical methods to describe an index of diversity. A secondary endpoint will be to determine differences in specific species or categories of bacteria between the groups.

Recruitment is currently ongoing for this study. The plan is to continue actively recruiting from the patient panel of the allergy immunology clinic, as well as to expand into affiliated Children’s Hospital clinics to recruit more allergic and control subjects. Stool samples are being stored for processing in the near future. When recruitment and examination of the stool microbiota is complete, statistical analysis will be performed to determine indices of diversity and differences in species prevalence. Secondary analyses may correlate species data to questionnaire results.

A main limitation of this study is that many of our control patients will also have some non-allergic atopic disease such as atopic dermatitis. Thus if differences in the microbiome are responsible for atopy more generally, we may not discover a difference between these populations. However as very little is known about the role of the microbiome in developing immune tolerance, this study represents an important initial step and can help generate hypotheses for larger and potentially prospective studies.
Malnutrition is a major public health challenge across much of the world, including in Haiti, and relief organizations are increasingly using ready-to-use therapeutic foods (RUTF) to rehabilitate children with acute malnutrition. The Partners in Health/Zanmi Lasante outpatient nutrition program operates at 11 sites throughout Haiti, and has been a pioneer in the local production of RUTF. Because the clinical use of this product is relatively new, it must be used with care. Routinely collected data and discussions with administrative and clinical staff suggest substantial differences in clinical processes, quality, and outcomes across PIH sites.

We began a quality improvement (QI) initiative focused on (1) patient flow in and through these clinics, (2) the ways in which clinical data is captured, recorded and analyzed, and (3) referral systems to various ZL programs that are related to outpatient nutrition. Our findings will inform improvements in the program.

We visited seven ZL nutrition clinics throughout the Central Plateau of Haiti, holding discussions with the head nutrition nurse at each site about quality of care, data gathering, and referral procedures, as well as informally observing clinical procedures. A Data Quality Audit (DQA) of clinical nutrition data collected and reported for three months in 2012 was also conducted at one site. Finally, a series of meetings was held with PIH/ZL administrators and staff from the Nutrition, Monitoring and Evaluation, and Informatics teams to discuss quality of care in the Nutrition program and ways to improve it.

These conversations focused on data collection and reporting, the development of new quality measures, and the feasibility of introducing a point-of-care electronic medical record in ZL outpatient nutrition clinics. An electronic medical record based on Haitian Ministry of Health paper forms was itemized, outlined, and proposed to the PIH/ZL informatics team.

Our final report will describe barriers to providing high quality of patient care, and will propose concrete strategies for overcoming those challenges. It will characterize current ways of collecting, reporting, and responding to data, and will include the results of our DQA. We will also propose ways to improve the collection and reporting of data, including outlining the rationale for developing and piloting an electronic medical record for ZL nutrition clinics. We may additionally propose ways to calculate new quality measures that can give program administrators valid and accurate quantitative information for evaluating and improving the program. Finally, we will describe how concurrent QI efforts in both clinical and data management can synergistically promote quality. We will also develop diagrammatic representations of data and patient flow in order to guide future improvements in the nutrition program.

This project has several limitations. Because this was a QI and not a research project, I was not able to collect data on or from individuals enrolled in the Nutrition Program or their caretakers and families. A language barrier prevented me from communicating directly with most Nutrition Program staff and administrators. Time to complete this project was limited and clinic visits were not comprehensive. I was unable to interview all staff at each clinic or to visit every clinic. Still, I developed good rapport with the PIH/ZL nutrition team. I am confident the insights gained this summer will be useful for guiding quality improvement in Nutrition Program moving forward.
CA4+: a Novel Cationic Contrast Agent for Evaluating Glycosaminoglycan Content by CT Imaging

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Osteoarthritis (OA) affects about 27 million people in the US. Unfortunately, OA is often diagnosed long after irreversible changes in the cartilage have transpired. This is because OA diagnosis is mostly empirical and because current imaging modalities focus on morphological changes of cartilage. Biochemical breakdown of cartilage occurs before morphological changes and symptoms are noticed. Importantly, loss of glycosaminoglycans (GAG) renders increased cartilage permeability, allowing increased water flow, and thus weaker cartilage. Our group has developed an unprecedented cationic contrast agent (CA4+) for CT imaging that can sensitively monitor changes in negatively-charged glycosaminoglycans (GAG), polysaccharide components of cartilage. This project investigates CA4+ in the human meniscus, a fibrocartilaginous structure implicated in knee OA.

Currently, Hexabrix is a contrast agent used for cartilage imaging. Not designed for cartilage imaging, Hexabrix is anionic and only renders an inverse representation of the GAG distribution in cartilage. We hypothesized that cationic CA4+ can predict the GAG content in human menisci with higher sensitivity than Hexabrix. To test this, this study compared the ability of CA4+ and Hexabrix to visualize meniscal GAG and quantified the sensitivity of CA4+ and Hexabrix at various times post-immersion.

Color maps of the CT attenuation in the menisci were generated for both Hexabrix and CA4+ at varying concentrations in comparison to a Safranin-O (GAG-specific) stained histology slide. CA4+ color maps mirrored the histology, indicative of CA4+’s selectivity for GAGs. An inverse GAG distribution was optimally seen with Hexabrix between 72 and 90 mgI/mL and a positive GAG distribution was optimally seen with CA4+ at 12 mgI/mL. R² values for CECT attenuation vs. %GAG were calculated using Hexabrix at 80 mgI/mL and CA4+ at 12 mgI/mL. For CA4+ at early times of 7hr and 9hr, high R² values of 0.67 and 0.60 were observed and at equilibrium (48hr), a very high R² value of 0.81 (p < 0.001) was observed, indicating CA4+ is able to explain the GAG variation in human meniscus. We also conducted simulated tear studies illustrating that exposed GAGs in radial tears could be highlighted within 3 hours post-immersion, confirming CA4+’s diagnostic relevance.

The development of CECT for quantifying meniscus GAG content will provide a high-resolution diagnostic for OA compared to radiography and MRI. Early diagnosis will slow OA progression, and CA4+ already holds great promise as a much-needed research tool to investigate new OA treatments with animal models without the need for harvesting animal joints.
Evaluating the needs of families and physicians of children with special health care needs

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Children with special health care needs (CSHCN, those who require health care beyond that required by children generally and who are at increased risk of chronic conditions) comprise 13-19% of all children, yet this group represents 80% of pediatric health care spending and presents with increased risk of medical errors, school absence, hospitalization and intensive care admission. With continually improving healthcare technology, the prevalence of CSHCN is on the rise. Furthermore, the gap between care quality for CSHCN and non-CSHCN is increasing.

In 2002, the AAP promoted the medical home as an optimal care model for CSHCN, arguing that “every child deserves a medical home.” The AAP defined a patient-centered medical home (PCMH) according to seven domains: primary care that offers accessible, continuous, comprehensive, family-centered, coordinated, compassionate, and culturally effective. Studies show that the more severe a child’s condition, the greater the benefit of a PCMH. Despite the strong theoretical support for the PCMH, implementation of the model has been slow, partly because most current fee-for-service policies fail to reward care coordination. Functional data demonstrating the PCMH’s value for CSHCN is needed to inform policy changes to overcome reimbursement and education barriers for PCMH implementation.

In a series of studies, we hope to evaluate the Boston Children’s Hospital’s Complex Care Service (CCS) as a hospital-based medical home. We will use three different survey tools, to evaluate the provision of the AAP’s seven core medical home tenets. The initial phase of the study will include a survey of families of CSHCN, which is part of a multi-center national study evaluating the needs of families of CSHCN. This will be followed by surveys of referring primary care and specialty providers. This summer the family survey was completed and is being sent out. When returned, the results will be examined with the outcome variable being the number of unmet needs identified. Also over the summer, the physician surveys and the IRB draft for the other two phases of the study were generated.

By defining the needs of the medically complex pediatric population, we hope to substantiate the medical home model and inform provision of comprehensive, coordinated care. Our results will be used to streamline our services and design an intake tool to improve the value of care provided. In addition to this local quality improvement, our findings will contribute to a broader understanding of how CCS programs can best be utilized in order to meet the needs of patients and physicians.
Evidence-Based Preventive Healthcare in the CWB Family Support Homes: The Healthy Learners Pilot Program

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Zambia is one of the poorest countries in the world. While most research has focused on children under 5, the school aged population experiences high mortality and morbidity rates from malnutrition, chronic and acute infections. Some of these infections include Schistosomiasis haematobium, hookworm, Plasmodium falciparum and HIV. Several publications support the claim that nutrition and health play a major role in preschool and school-aged children’s performance, attendance, and cognitive function.

Our long-term goal is to develop The Healthy Learners Program, an ongoing preventive health program for the NGO Community Without Borders (CWB) to supplement their mission among the school-aged children. The aim of the project was to pilot the program to help direct future efforts and determine feasibility of a permanent program. Pilot program activities included conducting health screenings at CWB family support homes, administering a detailed health status and needs survey, interviewing local experts and stakeholders, and conducting a health promotion workshop for teachers.

We employed a Zambian NGO, Angel of Mercy, to conduct the health screenings. All children who attended the screenings received height and weight measurements, vision screening, physical examination, urinalysis including examination for S. haematobium and urinary tract infections, vitamin A and Mebendazole, treatment for existing illnesses and BCG and tetanus vaccines as indicated. The health need assessment survey was conducted with the help of three medical students from the University of Zambia. Data was collected on paper, abstracted to deidentified forms and transcribed into a deidentified Excel file, which will be read into SAS for analysis. We will be able to identify baseline health information to focus on during future screenings.

In total we screened 458 children and surveyed 224 children with their guardians. Preliminary analysis of screening data reveals the most common health issues affecting the children screened to be urinary tract infections, upper respiratory tract infection, diarrhea, and fungal infection.

Of particular note, among the 458 children screened, there were 51 cases of S. haematobium. Although we were able to provide treatment for the infected children, an important next step for our program will be the development of communication strategies with local government clinics that can provide follow up care and home based education to prevent future reinfection.

Though detailed data analysis is pending, a finding from the health status survey is the lack of knowledge on health and sanitation topics and the urgent need to integrate health education in the school curriculum.
Oral Health Needs Assessment in Estancia, El Salvador

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Estancia is a cluster of communities in a rural, mountainous area in northeastern El Salvador. The local NGO, Campesinos para el Desarrollo Humano (Peasants for Human Development, CDH) works to alleviate health disparities and address unmet health needs for a population of approximately 2500 impoverished people through provision of medical care in their CAIPES (Centro de Atencion Integral, Prevencion y Educacion en Salud, Center for Integrated Attention, Prevention and Education in Health) and other public health projects. Dental care is an unmet health need in this area; there has never been accessible, affordable, appropriate, and sustainable dental care. The purpose of this project was to conduct an oral health needs assessment through dialogue with members of the community about their perception of need, knowledge, attitudes, and practices about oral health in Estancia. The project aimed to qualify the status of oral health in order to provide a foundation for further oral health initiatives.

We created the questionnaire with CDH staff and community health workers, trained them and conducted face-to-face interviews among a sample of people who entered CAIPES or lived in the nine caserios (communities) served by CDH. Interviews were conducted in CAIPES, during community meetings, and home visits. The questionnaire included information on sociodemographics, oral health practices, access to oral health care, oral health beliefs, and child oral health.

396 interviews were completed (34% of the total target population) and all data was entered into an excel spreadsheet. We will perform frequencies, Chi-square and t-tests to understand the prominent oral health problems in the communities, the current perceived system of services available, the extent of unmet needs, and underutilized resources or shortcomings of the current system.

This needs assessment will inform CDH in their planning of educational initiatives and integration of dental services in their local clinic. Based on our preliminary review of the data, we learned the following: parents reported that they tell their children the importance of oral health; respondents stated that the main barrier to accessing dental care was cost; and that the people of these communities desire dental care in CAIPES. Topics for an oral health curriculum for the community may include the importance of teeth (e.g. nutrition, appearance, speech), dental hygiene (including proper brushing technique and/or rinsing after eating), what to do about tooth decay, and dispelling myths about oral health (e.g. iron supplementation damages teeth, primary teeth not being important).
Tracking and Improving Transitions of Care within a Patient-Centered Medical Home

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Hospital readmissions reflect poor patient outcomes and cost billions of dollars annually. Poor transitions between hospitals and outpatient settings may be fueling this trend. The quality improvement project aimed to improve patient outcomes following hospital discharge in a patient-centered medical home by improving critical practice-level data feeds on admissions, determining which patients are at highest risk of readmission, and identifying the limits of current care transition interventions.

Brigham and Women’s Advanced Primary Care Associates, South Huntington is a patient-centered medical home designed to foster team-based care, experimentation and creativity in health care delivery, and real-time evaluation. South Huntington’s interventions to reduce hospital readmissions include touching base with patients in the hospital, conducting post-discharge visits within 72 hours of discharge, performing personalized case management by an on-site nurse care coordinator, and offering interdisciplinary (PCP, pharmacist, social worker, nutritionist, etc) post-discharge care. The quality improvement project has supported this by setting up systems to: 1) Monitor outcomes using data feeds to calculate admission, readmission, and ED visit rates and use results to identify potential care transitions process improvements; 2) Evaluate quality of data availability on high-risk patients; 3) Map and evaluate the current post-discharge process, and 4) Perform a readmissions taxonomy.

To date, we have established baseline admission, readmission, and ED visit rates and have identified gaps in the admissions tracking system and in critical information flows between the hospital and the clinic. It appears that overall hospital admissions and ED visits are trending downward. Results of the data collection and readmissions taxonomy thus far suggest that while the patient-centered medical home has the potential to reduce inpatient utilization, cultural and institutional change takes time. Patience is needed to go through cycles of experimentation, evaluation, and iterative adjustment. Lessons from this project are limited to primary care practices with sufficient resources and motivation to manage high-risk patients in an interdisciplinary, team-based manner. We also expect to learn further lessons about the process metrics most closely tied to readmissions and to have a better understanding of the viability of readmissions rates as an effective metric. We have seen that patient factors such as substance abuse and behavioral health problems, along with those that fall outside the purview of the health care delivery system (unemployment, family stress, community violence, etc.), put patients at higher risk of readmission and demand creative solutions beyond the typical scope of the current health care delivery model.
Prevention of Mother-to-Child Transmission HIV and Syphilis: The Health Professional’s Role

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The Caribbean is the second most HIV affected region in the world after Sub-Saharan Africa, with the majority of cases concentrate in Hispaniola and heterosexually transmitted (Global HIV/AIDS Response Progress Report, 2011). In the Dominican Republic, young women, especially of lower education level and living in bateyes-isolated communities, are disproportionately affected by HIV (Global Health Initiative, 2012). The high numbers of HIV infections among women in the Dominican Republic who are of reproductive age negatively influence both HIV and syphilis mother-to-child transmission rates and maternal mortality rates (Center for Health and Gender Equity, 2009). The Prevention of Mother-to-Child Transmission (PMTCT) effort is vital to both reducing HIV and Syphilis infection among children and reducing maternal mortality.

Although recent collaborations between Harvard Medical School, UNICEF and local organizations (CENISMI, COPRESIDA and DIGECITSS) reviewed the weaknesses of the national PMTCT program (Integración de la Atención Prenatal con los Procesos de Detección y Manejo Clínico del VIH y de la Sífilis en la RD, 2011), no knowledge or adherence surveys with health professionals were conducted. Furthermore, most PMTCT research concentrated in the capital area. This study in Santiago, the second largest city in the country, provides an important addition to the local PMTCT effort. As the Dominican Republic has a set of national guidelines for handling prenatal HIV and Syphilis transmission, it is vital to continuously evaluate the knowledge and access of both health professionals and patients to these guidelines and resources.

This study included observations and a survey examining HIV PMTCT knowledge and national guideline knowledge among residents of four departments at the general public hospital in Santiago: OB/GYN, perinatology, neonatology and HIV. The observations were carried out first to get acquainted with health professionals’ roles and work flow. The national flowchart of HIV diagnosis and treatment in pregnant women was used as the guide for evaluating PMTCT knowledge and appropriate care. The anonymous and confidential surveys included 27 questions examining general PMTCT knowledge and PMTCT guideline knowledge during prenatal care, labor, and postnatal and newborn care. A comprehensive training session about HIV and syphilis PMTCT was given to all interested residents after the conclusion of data collection.

The preliminary assessment of the data showed varying degrees of training, education and knowledge of PMTCT guidelines among participating residents. Most, but not all, questions demonstrated improved knowledge with increased training. According to the data, despite the existence of national PMTCT guidelines and periodic training sessions, 22 out of 53 residents never received PMTCT training and do not have the appropriate knowledge to take care of HIV positive pregnant women and their newborns. More in depth and frequent training sessions are needed for the improved integration of prenatal care and HIV and syphilis prevention and treatment.
Disease Management of Early Childhood Caries: Part II

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Early childhood caries (ECC) continues to be the most common chronic condition among children in the United States, with prevalence in 2-5 year old children having increased 15% to 28% in recent years. The concept of caries management is based on the idea that dental caries is a largely preventable disease. Certain measures such as changing oral bacteria, reducing the dietary intake of sugar, decreasing eating frequency, adding fluoride into toothpaste, and increasing salivary flow can change the biochemistry. This process of changing the local biochemistry can help to prevent the caries in the patient instead of just restoring the cavities because restorative treatment only repairs the damage; it does not prevent future disease.

The purpose of this study was to continue monitoring the outcome of patients selected in an previous study to see if the disease management protocol that was set up sustained in preventing ECC’s in a long-term setting. The goal of this project was to assess the effects of a long-term disease management protocol that has previously been put in place. Overall the intervention is to teach parents and patients about dietary changes and in-home use of fluoride that could potentially help reduce the long-term risk of caries. The hypothesis of part I and II of the study was that by educating parents and patients about the cause of caries and some preventative for causing caries (such as diet and fluoride use), the number of early childhood caries could be reduced.

The project was implemented as a quality improvement project. The project began on March 1, 2008 and ended on September 30, 2010. 403 patients were enrolled in the study and received the disease management protocol. The control group was a historical control from a retrospective chart review. The patient’s caries risk and overall caries assessment was recorded via Caries Assessment Tests (CATs) in an Access database. Part I collected data for 30 months and part II collected data for 48 months. The data was analyzed by a biostatistician using a p-value < 0.05 to measure significance.

The results of part II were that the long-term prevention of ECC’s was significant for the patients enrolled in the disease management protocol compared to the control.

This study supported the idea that the disease management protocol sustained long-term prevention of ECC’s. The results suggest that implementing a disease management protocol in pediatric dental clinics can potentially prevent ECC’s.
A microfluidic device to process sputum for the downstream detection of Tuberculosis

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Each year, almost 9 million people worldwide contract tuberculosis (TB) and nearly 2 million die from TB-related causes. A major obstacle to TB control in resource-limited countries is the lack of an effective diagnostic test that can be used for point-of-care (POC) testing.

Our research team is working on a microfluidic sample processing platform and a miniaturized nuclear magnetic resonance system for clinical POC diagnosis of TB. The team has made significant advances in the development of the microfluidic device as well as improvements in the sensitivity of the detection system, however a remaining major challenge is the incomplete pre-processing of the initial clinical sample (sputum), which causes clogging of the device’s microchannels and limited release of the Mtb bacilli from the sputum matrix.

Sputum is highly viscous, comprising of eukaryotic cells and a large number of oral flora bacteria, all within a highly crosslinked protein matrix. We hypothesized that treatment of sputum with the mucolytic agent N-acetyl-L-cysteine (NALC), and with the decontaminant sodium hydroxide (NaOH) will yield a fluid that is amenable to microfluidics handling and will contain the majority of the Mtb bacilli that is present in the original, pre-processing sample. To test this hypothesis, two specific aims were addressed. The first aim was to obtain a sample with less than 5 cP viscosity, free of particles larger than 10 μm, and in a volume of less than 10 mL. The second aim was to remove greater than 90% of non-target bacteria to yield a sample with greater than 80% intact Mtb.

De-identified sputum samples from MGH were successfully liquefied with 0.5% NALC-2% NaOH and 5X phosphate buffer, based on their ability to pass through a 70μm strainer and a 10μm filter. The pH of the processed sputum samples was 7, which is crucial for antibody binding in the subsequent detection steps. Additionally, 5/5 processed sputum samples ran through the microfluidic platform without clogging the 10μm microchannels. Based on the reduction in growth of non-target bacteria on trypticase blood agar plates, it appeared that the decontaminant was successful in killing greater than 90% of non-target bacteria. Whole-cell ELISA revealed that NALC-NaOH does not destroy surface antigens on BCG.

In the future, we need to quantify the release of BCG during sputum processing using quantitative PCR. Finally, all these assays need to be repeated with Mtb either as spiked experiments or directly with frozen sputum samples from TB patients.
Mobile HIV testing at community venues may allow for HIV/AIDS diagnosis in individuals who are asymptomatic and have consequently not accessed screening services at healthcare facilities. By identifying HIV infection at an earlier stage, mobile testing may be leveraged to initiate earlier treatment and prevent further transmission. This study aims to quantitatively assess rates of linkage to care for individuals receiving new HIV diagnosis at mobile and clinic-based testing sites in Durban, South Africa.

Ithembalabantu Clinic offers free HIV testing at sites such as taxi stands and shopping malls in the Durban area. Individuals testing positive either within the clinic or at mobile sites are offered CD4 count testing as the first step in the linkage to care pathway. All adults (greater than 15 years of age) receiving HIV tests at Ithembalabantu mobile sites and clinic from July-October of 2011 were prospectively enrolled in this study. We obtained subject demographic information from intake forms and measured the primary outcome for linkage to care as the proportion of subjects returning for CD4 count results at Ithembalabantu Clinic within 12 weeks of a positive HIV test.

From July-October of 2011, 6,957 subjects were tested (4,703 at mobile sites and 2,254 in clinic). Subjects tested at mobile sites exhibited a lower prevalence of HIV (10% versus 30%), were younger (mean age of 27 versus 30 years), and were less likely to undergo CD4 testing (32% versus 84%). Of the subjects who underwent CD4 testing, mobile testers were more likely to have CD4 counts ≥200 /µl (89% versus 64%) and exhibited higher median CD4 counts (416/µl, IQR 287-587 versus 285/µl, IQR 136-482, p<0.001). Of subjects with CD4 counts, only 10% tested at mobile sites linked to care as compared to 72% of subjects tested in clinic (p ~0.001).

Our findings indicate that individuals who test for HIV at mobile sites are younger, less likely to undergo CD4 testing, and have higher CD4 counts than individuals tested within a clinical context. The rate of linkage to care was ultimately lower for individuals tested at mobile sites. Though mobile testing shows potential for identifying HIV/AIDS at an earlier stage, further research is needed to facilitate linkage to care.
Neuroimaging Markers of Treatment-Associated Neurotoxicity in Glioblastoma Patients Undergoing Brain Radiation and Temozolomide Chemotherapy

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Systemic chemotherapy and brain irradiation are associated with neurocognitive impairment detectable in cancer patients during and after treatment. Up to 70% of cancer survivors experience higher-order cognitive deficits, significantly affecting patients’ ability to perform at pre-treatment levels in their personal and professional lives. Adult neurogenesis plays a key role in maintaining and remodeling the cytoarchitecture of the brain’s neurocognitive networks, with neural progenitor cell (NPC) pools in the hippocampal dentate gyrus and subventricular zone (SVZ) giving rise to neurons and glial cells throughout the adult lifespan. Preclinical studies have demonstrated that NPCs are particularly vulnerable to chemotherapy and radiation, but in vivo biomarkers of neurotoxicity in humans have not been established. Here, we used structural and diffusion-weighted magnetic resonance imaging to explore patterns of neurotoxic injury to a cohort of patients undergoing chemotherapy and radiation therapy for glioblastoma (GBM).

We longitudinally examined neuroimaging parameters within germinal zones and non-tumor regions in 14 GBM patients receiving daily temozolomide (TMZ) chemotherapy and brain irradiation over six weeks, followed by up to 6 monthly cycles of TMZ. We used high-resolution MEMPRAGE structural images to assess ventricular and hippocampal volume changes, and diffusion-weighted imaging (DWI) to assess changes in apparent diffusion coefficient (ADC), a marker of free water movement and cellular density, within hippocampus and SVZ.

Subjects remaining in treatment beyond the 6-week chemoradiation period (N=12) showed mean ventricular dilatation of 39.0% (SD: 22.0%; range: 6.8-67.1%) at final visit. Percent volume change was positively associated with duration of exposure to treatment, and was not associated with tumor volume changes. SVZ ADC values were available for 11 subjects in treatment beyond chemoradiation and showed more variability. Mean percent change at final visit was 42.4% (SD: 43.4%; range: -10.2-114.4%). We found no significant changes in hippocampal volume or ADC.

We present evidence of non-tumor-associated brain changes over the treatment period in brain regions critically relevant to neural progenitor populations and maintenance of adult brain plasticity. Neurotoxic injury to the SVZ may cause periventricular tissue loss and diminished capacity for neurogenic repair. Ongoing studies include analysis of changes in whole-brain volume and parenchymal white matter ADC. In addition, we will further validate our findings in an independent GBM cohort undergoing a similar therapeutic regimen. Available neurocognitive measures were insufficiently sensitive to test longitudinal changes in cognitive status, necessitating future prospective trials to assess the relationship between treatment-associated brain changes and long-term cognitive outcomes.
Demographic Characteristics and Progression of PPMS in the CLIMB Study Population

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Background: Primary progressive multiple sclerosis (PPMS) is found in 10-15% of the MS population and has the worst prognosis of MS subtypes. Updated understanding of PPMS disease progression, especially in the era of disease modifying therapy, is important to improve clinical care and for designing randomized clinical trials in this population.

Objectives: To characterize demographic and clinical characteristics of the CLIMB study (Partners MS Center, Boston, MA) PPMS patient cohort and assess the rate of PPMS disease progression, clinically evaluated by Expanded Disability Status Scale (EDSS).

Methods: Longitudinal prospective data was collected from the CLIMB study for all PPMS patients (n=80) and a representative sample of relapsing-onset MS patients (n=426, disease onset 2005-2010). Cross-sectional analyses compared PPMS and relapsing-onset (RO) groups. In each group, the time from disease onset to first EDSS 3 (Phase 1), from first EDSS 3 to first EDSS 6 (Phase 2), and from onset to first EDSS 6 was assessed using interval censored survival analysis. Also, time to 6-month sustained progression in PPMS patients was analyzed using traditional survival analysis.

Results: The PP group had a 1:1 male:female ratio, higher than the RO group (RO: 1:3.14; p<0.001), and a greater mean age of onset (PP: 44.83+/−9.68; RR: 33.95+/−10.92; p<0.0001). Presence of sensory symptoms at onset was strongly associated with PPMS (p<0.001), as was spinal cord localization of first symptoms (p<0.001). Overall, median time from onset to EDSS 6.0 was faster in PPMS patients vs. RO patients (p<0.001). The PPMS patients progressed faster through Phase 1 (p<0.001) and through Phase 2 (p<0.005). Median time to sustained progression in the PP group was 4.39 years (95% confidence interval: 2.74-6.77), and this was significantly faster than in the RR group (p<0.001).

Conclusions: Our PPMS cohort from the modern treatment era is demographically similar to previously studied cohorts. We found that faster progression through Phase 1, Phase 2, and from onset to EDSS 6 is associated with PPMS. Reevaluation of time to sustained progression provides a basis for design of new clinical trials in PPMS.
The role of AKT signaling in T-cell acute lymphoblastic leukemia relapse

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Thousands of children and adults in the United States are diagnosed with T-cell acute lymphoblastic leukemia (T-ALL) annually. Less than 30% of children and 8% of adults will survive relapsed T-ALL. While relapsed leukemia is often more aggressive and treatment resistant than primary disease, the genetic and molecular mechanisms underlying relapse are not well understood. Recent work from the Langenau laboratory has shown that relapsed T-ALLs acquire mutations that activate the AKT signaling cascade, ultimately increasing leukemia aggressiveness and increasing the numbers of cells capable of driving relapse growth. The focus of this project was to determine which downstream AKT targets regulate leukemia propagating cell (LPC) frequency, determine whether AKT provides a selective advantage to LPCs and mediates drug resistance, and determine which upstream regulators activate AKT in evolved clones.

Both in vivo and ex vivo leukemia cells are being treated with drugs that inhibit downstream AKT pathways to determine which targets are necessary for increased LPC frequency and aggression. Prior to beginning this experiment, it was necessary to determine the best method for engrafting leukemia in embryonic fish. To do so, I transplanted fluorescent-labeled T-ALL cells into four different anatomical locations in zebrafish at four different stages of development. I concluded that injecting approximately 4x10^4 cells into the sinus venosum of 2-day-old embryonic fish was the most effective method of introducing leukemia. Additionally, I optimized dosing of embryonic zebrafish with drugs that inhibit AKT, p53, mTOR, β-catenin, and NFKβ. Ongoing experiments are being completed to assess which drugs modulate growth and relapse in the zebrafish T-ALL model.

Working with Dr. Jessica Blackburn, we have also undertaken experiments to treat T-ALL cells ex vivo with chemical inhibitors. During the fall of 2012, I will monitor the survival of leukemia cells both with and without activated AKT for 48 hours after drug treatment. Initial experiments indicate that mTOR may be an important downstream pathway, but drug dosing needs to be further optimized. I will also use ex vivo drug treatments to determine if activated AKT mediates dexamethasone resistance in relapsed T-ALL. Leukemia cells with and without activated AKT will be treated with dexamethasone, a commonly used T-ALL drug, and with dexamethasone plus AKT inhibitor. Finally, I am using PCR and real-time PCR to determine what upstream regulators of AKT are involved in its activation. I will sequence commonly overexpressed activators and look for mutations that may be involved in AKT activation.
Treatment Outcomes in Patients with Van der Woude Syndrome and Popliteal Pterygium Syndrome

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Van der Woude syndrome (VWS) and popliteal pterygium syndrome (PPS) are allelic autosomal dominant disorders caused by mutations in interferon regulatory factor 6 (IRF6). They comprise the single most common syndromic cause of cleft lip and/or palate (CLP), accounting for 2% of all cases. VWS is characterized by CL and lower lip sinuses; PPS has the same features plus popliteal webbing, genital malformations, and syngnathia.

This was a retrospective review of the medical records of all patients with VWS/PPS seen at a tertiary care center from 1979 to 2012. Age, sex, family history, cleft type, operative procedures, speech outcome, and midfacial growth were documented. These data were compared to patients with nonsyndromic CLP treated at the same tertiary care center.

The study included 28 patients with VWS (n=21)/PPS (n=7): 18 patients (64%) were female and 18 patients (64%) had a positive family history of VWS/PPS. One patient (4%) had isolated bilateral complete cleft lip, 1 (4%) had occult submucous cleft palate, and 2 (7%) had lower lip sinuses only. Among the 24 patients with cleft palate, Veau types I, II, III, and IV were found in 4 (17%), 4 (17%), 5 (21%), and 11 patients (46%), respectively. Among the 20 patients with Veau type II-IV cleft palate, 10 (50%) had hypoplastic hard palatal shelves; 9 (38%) of the 24 with Veau type I-IV cleft palate had palatal fistula. Of the 23 patients age 4 or older with Veau type I-IV cleft palate, 10 (40%) required a pharyngeal flap to manage velopharyngeal insufficiency. Of the 23 patients age 5 or older with Veau type I-IV cleft palate or isolated cleft lip, 14 (61%) had midfacial retrusion.

Clefting characteristics and treatment outcomes for patients with VWS/PPS were compared to existing data for patients with nonsyndromic CLP. Using chi-square analysis, the distribution of Veau types was found to differ from that of nonsyndromic patients (p=0.03), with a higher incidence of type IV clefts and a lower incidence of type III clefts in VWS/PPS. Using Fisher’s exact test, the incidence of palatal fistula (p<0.0001), midfacial retrusion (p=0.0001), and the need for a pharyngeal flap (p=0.0014) were higher among patients with VWS/PPS.

Patients with VWS/PPS have more severe forms of oral clefting and higher incidences of impaired speech, palatal fistula, and midfacial retrusion. These findings may help clinicians to counsel families and plan long-term interdisciplinary care for patients with these disorders.
Safety of Outpatient Hip Arthroscopy as Compared to Inpatient Admission

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Consistent pressures to reduce cost and efficiently use inpatient facilities have lead to a push for outpatient care in the United States. Despite widespread performance of hip arthroscopy on an outpatient basis, no study exists establishing the safety of this practice. The goal of this study was to evaluate the utility of overnight hospital stay following hip arthroscopy as compared to same day discharge.

After IRB approval, a retrospective review of prospectively collected data from the first consecutive 100 cases of a single fellowship trained surgeon (JJC) was performed. All patients presenting for hip arthroscopy after failure of conservative care were included. Revision cases were excluded. Subjects were separated into the first 50 operative procedures admitted overnight for observation and examined in the hospital the first postoperative day and the second 50 operative procedures discharged same day postoperatively and examined in the office postoperative day one. All patients received standard postoperative protocol. We compared patient reported complaints, examiner noted complications, and improvement in modified Harris Hip Score at 6 weeks and 3 months.

Complete data for complications existed for all 100 subjects. There were no major complications (death or problem requiring readmission) in either group while minor complications (superficial infection, syncope, constipation, neurapraxia) were not statistically different in either group. Complete data for patient recorded outcomes was available for 18/50 inpatients and 13/50 outpatients. Preoperative mHHS values were 54.1±15.1 and 64.2±12.8 for inpatient and outpatient, respectively. Six week MHHS for inpatient (79.5±20.1) versus outpatient (88.3±16.5) as well as the three month MHHS for inpatient (88.3±16.5) compared to outpatient (86.0±13.5) showed no statistical difference between groups by independent t-test with α at 0.05.

This retrospective study suggests that hip arthroscopy can be performed safely with outpatient discharge the same day as surgery and early outpatient follow-up.
Head and neck squamous cell carcinoma (HNSCC) is the third most prevalent cancer worldwide with more than 600,000 cases diagnosed annually. HNSCC has a complex etiology that includes lifestyle behaviors, classical chemical carcinogenesis, and infection with high-risk human papilloma viruses (HPV). HPV(+) head and neck cancer patients have a more beneficial micronutrient profile, increased responsiveness to treatment, and improved overall survival compared to HPV(-) head and neck cancer patients. HPV(-) patients generally have a more remarkable history of tobacco and alcohol use.

Methylation of tumor suppressor genes is a common genetic defect found in head and neck squamous carcinoma and is believed to be responsible, in part, for cancer cell proliferation. It has previously been shown that HPV(+) head and neck cancers have a distinct epigenetic profile when compared to HPV(-) cancers by comparing CpG site methylation for candidate suppressor genes in DNA extracted from the tumor microenvironment. An ongoing study is determining correlations between the methylation status of candidate tumor suppressor genes and tumor behavior, patient smoking status and outcome. In a clinical setting, these methylation markers can help monitor the treatment and tumor recurrence for patients diagnosed with HNSCC.

We hypothesize that circulating DNA in the patient’s serum may have methylation markers that could be surrogates for gene methylation in a patient’s tumor. The ability to monitor gene methylation status using serum as a surrogate for tumor tissue would provide great utility in the clinical setting. The project explores methodology for assessing DNA methylation in sera and identifies correlations with DNA methylation of tumor suppressor genes. To test this hypothesis, we identified 50 patients—41 HPV(+), 9 HPV(-)—with oropharyngeal HNSCC. DNA extracted from their sera was subjected to bisulfite conversion. Bisulfite converted DNA underwent pyrosequencing analysis to determine CpG site methylation in candidate genes. These genes are involved in pathways regulating cell cycle progression, apoptosis, DNA repair and tumor invasion.

Preliminary data indicate that methylation patterns can be detected in circulating DNA for some of the tumor suppressor genes analyzed. Pyrosequencing analysis of the candidate suppressor genes using DNA extracted from tumor tissue was previously completed for these 50 patients. We must now compare the methylation in tumor DNA to the circulating DNA from patient sera to determine whether gene methylation in sera can act as a surrogate for tumor tissue.
Alcohol Intake and Risk of Incident Melanoma: A Prospective Study

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Melanoma incidence in the United States rose at an average rate of 3% per year between 1975 and 2009. As a result, Americans born today have a roughly 1 in 50 chance of being diagnosed with melanoma in their lifetime, compared to 1 in 1500 for Americans born in 1935. Similar trends have been documented throughout Europe, Australia, and New Zealand. Thus, melanoma prevention has become a major public health concern.

Traditional risk factors for melanoma include age, red/blond hair colour, fair skin, personal or family history of skin cancer, presence of numerous or atypical moles, immunosuppression, and UV radiation exposure. Of the known risk factors, only UVR is modifiable. Other proposed risk factors, including diet, smoking, and alcohol intake, have not been definitively linked with melanoma.

We hypothesized that alcohol intake is associated with melanoma, and that the effects of alcohol intake may be dependent on beverage type. To test this hypothesis, we analysed data from three large prospective cohort studies: the Nurses' Health Study I, Nurses' Health Study II, and Health Professionals' Follow-Up Study. Follow-up was via questionnaires sent out at two-year intervals, with >90% response rate in each cycle for all three cohorts. Statistical analysis was performed using the Cox proportional hazards model to estimate relative risk (RR), with variables updated every two years. Participants reporting non-white ethnicity or a history of cancer were excluded. The exposures of interest were total alcohol intake and beverage-specific alcohol intake (light beer, non-light beer, red wine, white wine, liquor). The outcomes were incident invasive melanoma and incident melanoma in situ. Covariates included age, red/blond hair colour, family history of melanoma, number of moles, UVB flux at place of residence, number of severe sunburns, skin reaction after 1 hour in the sun, and smoking history. Beverage-specific analyses were additionally adjusted for total alcohol intake.

Preliminary results show that total alcohol intake is positively associated with invasive melanoma and that white wine has an alcohol-independent association with invasive melanoma. Non-light beer was associated with invasive melanoma in men, but not in women. These results were not sensitive to exclusion of lentigo maligna melanomas. Results for melanoma in situ are consistent with those for invasive melanoma, but are mostly not statistically significant. There was no effect modification by age, BMI, smoking history, or caffeine intake.
Generation of Anti-Treatment Antibodies in a Mouse Model of Osteogenesis Imperfecta

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Osteogenesis imperfecta (OI) is a heritable bone disorder that causes skeletal fragility and progressive deformity. OI affects 1 in 10,000 newborns. The severity of the OI phenotype depends greatly on the mutation and can vary from having a minimal effect on life to severe debilitation. Current treatment for OI is of limited clinical efficacy and has potential drawbacks, pointing to an urgent need for a safe, effective therapy for OI.

Previous studies have identified a monoclonal antibody, anti-SOST antibody, that promotes bone production through the Wnt/β-catenin signaling pathway. This antibody has been shown to increase bone strength and mass in mice models of OI and is thus a promising therapy for OI. However, as a foreign protein, this monoclonal antibody has the potential to generate anti-treatment antibodies, which have the potential to decrease therapeutic effectiveness by inducing immunogenic treatment resistance. The extent to which this occurs in response to anti-SOST injection remains unknown.

We hypothesize that the administration of anti-SOST antibody to adult mice will generate anti-treatment antibodies. Because the anti-SOST antibody used in these experiments is a rat antibody, its administration has the potential to generate anti-heterotype antibodies. Using ELISA assays for anti-SOST and anti-heterotype antibodies, we quantified the generation of anti-treatment antibodies in adult mice treated for various times, from six weeks up to three months. Preliminary data suggest that administration of rat anti-SOST antibody to adult mice increases the generation of anti-heterotype antibodies, proportional to the timecourse of antibody administration. These results suggest that for anti-SOST to be effectively used as a therapeutic antibody, which necessitates continual administration throughout life, immunologic reaction may be significant. This provides compelling rationale to study prenatal administration of anti-SOST antibody to induce immunologic tolerance, potentially increasing the therapeutic effectiveness of the treatment.
Are Lower Rates of Spending Growth Here to Stay? Analyzing the National Spending Slowdown 2007-2010

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Background: Between 2008-2010, national healthcare spending grew at record low rates of 3.9 and 3.8 percent, respectively. Slow growth among privately insured individuals significantly influenced this moderation. Several policy experts have speculated that this slowdown is primarily attributable to the global economic recession, implying that high rates of spending growth will resume as the economy recovers and that the nation needs better spending control policies. Conversely, multiple prominent economists have postulated that the low growth rates are attributable to decreasing insurance generosity; this could imply a long-term slowdown which outlasts the recession. Recent literature, which traces the beginning of the slowdown to before the recession, supports the latter hypothesis. To analyze the impact of the recession versus changes in insurance generosity in slowing spending, we model healthcare spending from 2007-2010 as a function of state unemployment rates and insurance generosity. Our results will shed light on whether the slowdown is likely to be temporary, or whether we may see sustained slower growth in national healthcare spending.

Methods: We use the 2007-2010 Truven Health Analytics Marketscan Commercial claims data set for our analysis. Our sample includes enrollees in plans with over 1500 enrollees and excludes enrollees with capitated claims. For consistency we only include data from employers who submitted claims over the entire study period. In our models, we use enrollee-level fixed effects to control for inter-enrollee variation. Our unit of analysis is the person-quarter; accordingly we include unemployment data at the state-quarter level from the Bureau of Labor Statistics. As measures of plan generosity, we include variables for the plans’ quarterly average ED visit copay, average branded drug copay and average deductible payment. All models are adjusted for age, sex and seasonality. Our sensitivity analysis includes testing models with predictor variables in isolation, as well as in combination.

Results: In our data, spending slowed from 5.3 to 2.0 percent during 2007-2010. Additionally, average deductibles (p<0.000), but not average ED or branded drug copayments were a significant driver of the slowdown. State unemployment levels may have contributed to the slowdown (p=.263). Results were not sensitive to including only subsets of predictor variables.

Discussion: The spending slowdown among the privately insured appears to have been driven by rising deductibles, as opposed to other out of pocket payments or unemployment levels. This may signal a more permanent slowing of spending growth, in which case the politically daunting economic forecasts are overstated.
Understanding Arm Fractures in Young Children: Abuse or Not?

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Fractures are the second most common injury seen in the over 125,000 children who are physically abused each year. Unfortunately, distinguishing between fractures caused by abuse and those not caused by abuse can be difficult. Although many studies have developed guidelines for determining the etiology of fractures, few specifically address arm fractures. In the absence of guidelines, evaluating the cause of arm fractures has the potential to be variable and biased.

We therefore aim to describe the characteristics and circumstances of upper extremity fractures in young children. Electronic medical records were reviewed for all patients <18 months old who presented with radius, ulna, and/or humerus fractures between September 2007 and January 2012 to two large, urban hospitals, excluding children with conditions predisposing for bone weakness. Demographic information, presenting histories, and fracture types were described and then compared across the subset of children evaluated for abuse by the hospital child protection teams (CPTs).

The 226 eligible patients had a median age of 13 months and half were female. They sustained 321 arm fractures total. The most frequently fractured bone was the radius (n=131, 58%), followed by the humerus (n=97, 43%) and ulna (n=84, 37%). Falls were described as causing 72% of the fractures. Of the 85 patients evaluated by the CPTs, 31 (37%) were determined to have injuries caused by child abuse and 45 (53%) were determined to have non-inflicted injuries. Children identified as abused were significantly younger (median age = 5 mos. vs. 11 mos.; p< 0.001) than children with non-inflicted injuries. A fall was the most common reported history for patients with non-inflicted forearm and humerus fractures (74% and 67% respectively), while either no history of trauma or a changing history was provided if the forearm and humerus fractures were determined to have been inflicted (100% and 67% respectively).

In conclusion, the absence of a history to explain an injury in a young child who is not yet cruising, a changing history, and young age should all increase the physician’s suspicion that an upper extremity fracture was caused by child abuse.
Antibiotic Selection for ORIF of Mandible Fractures

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Many mandible fractures are treated using open reduction internal fixation (ORIF) due to its superior stabilization of the fracture line, better healing, and faster recovery while minimizing the duration of immobilization of the mandible. However, ORIF requires an incision and placement of hardware, which can lead to one of the most common complications of a mandibular fracture repair: postoperative wound infection. Such infections have been shown to delay healing and cause malunion, greatly increasing cost and morbidity for the patient and the health care system.

Historical controls have shown the infection rate after such surgeries to be anywhere from 6% to 32%. Most of the infections are due to normal oral flora, which is a mix of diverse facultative and obligate anaerobes. We believe that the average infection rate of 12.6% in historical controls is unacceptably high and hypothesize that use of a broader-spectrum antibiotic regimen to cover normal oral flora will decrease the number of surgical site infections in ORIF mandible fracture repair. The purpose of this retrospective study is therefore to determine the proper antibiotic prophylaxis and generate a recommendation for the future.

A retrospective review of 79 patients treated with ORIF mandibular repair was completed. Six infections were identified, giving a total infection rate of 7.59%. Patients treated with clindamycin had an infection rate of 19.35%. The infection rate when using ampicillin/sulbactam was significantly lower than clindamycin.

On the basis of this review, proper antibiotic prophylaxis should cover both potent aerobes and anaerobes. Due to the ease of use, great coverage for potential pathogens, low cost, and limited side effects, we recommend the perioperative use of cefazolin plus metronidazole for ORIF treatment of mandible fractures. However, due to the potential alcohol interaction and subsequent post-operative compliance with metronidazole, we recommend postoperative amoxicillin/clavulanic acid due to its broad spectrum and similar mechanism of action to I.V.-administered ampicillin/sulbactam, which returned favorable results in this study.

However, we recognize that resistance among bacterial isolates may show clinically important differences between countries, geographic regions, and even hospitals. Given that ours is a teaching hospital in a metropolitan area, we are bound to see a wider variety of bacterial isolates and resistance patterns. Finally, while the antibiotics here are limited to those prescribed by surgeons, a wider variety of antibiotic choices does exist. Despite these limitations, we believe our recommendation is credible and will aid in reducing infection rates associated with this surgical procedure.
Long Term Complications of Open Staple vs. Endoscopic Zenker’s Surgery

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Zenker’s diverticulum (ZD) is the herniation of mucosa into the space between the transverse fibers of the cricopharyngeus and the oblique fibers of the lower inferior constrictor. Excessive pressure results in an outpouching of the pharynx. The incidence of ZD in the general population is 0.01% to 0.11%. These patients experience dysphagia as food becomes lodged in the diverticulum. This leads to the subsequent risks of regurgitation, chronic cough and, most seriously, aspiration pneumonia.

Current literature on the treatment of ZD heavily favors the use of endoscopic procedures over external surgical techniques, arguing that endoscopic approaches reduce intraoperative time and anesthesia, length of hospital stay, and days until oral diet is restarted. However, such techniques often have higher symptomatic recurrence rates and require further interventions. Because of our experience with both endoscopic diverticulotomy and external diverticulectomy using the GIA-stapler, we sought to compare these two procedures in terms of in-hospital parameters, complications, return to normal diet, and rates of symptom recurrence.

In this study, we retrospectively analyzed 70 patients at Brigham and Women’s Hospital who underwent either an endoscopic procedure (36) or an external stapler-assisted diverticulectomy with cricopharyngeal myotomy (34). The patient group is a relatively small sample size, but with proper statistical analysis, we hope that this comparison of the two surgeries at the same center will prove beneficial in the literature. Another limitation is that this is not a randomized study: the selection of which patient receives which surgery is based on patient preference with physician counsel.

We have collected and input all the patient data and done a preliminary review of it, but will start next week with the statistical team to conduct a formal analysis. Although the external stapler-assisted procedure for ZD does carry a longer intraoperative time, it provides similar days until initiation of an oral diet and a slightly longer hospital stay. The extended intra-operative time of the external technique does not appear to cause a higher incidence of anesthesia-related complications. The incidence of serious complications, mainly pharyngeal perforation with leak, is lower in the external approach. It is superior to the endoscopic approach when one considers the symptomatic recurrence or persistence of ZD and need for revision procedures.

We argue that the external stapler-assisted diverticulectomy with cricopharyngeal myotomy may in fact be considered as a viable treatment in elderly patients who need definitive, single-session treatment for ZD to prevent life-threatening aspiration and pneumonia.
Cardiac allograft vasculopathy (CAV) develops frequently in heart transplant recipients and remains a major limitation to long-term survival. CAV consists of a concentric diffuse intimal thickening of the arterial walls of both epicardial and intramural coronary arteries with resultant myocardial ischemia, infarction, and allograft failure. Although non-immune factors are present, alloimmune mechanisms likely predominate since CAV is limited to allograft tissue. Multiple immune cells, including T cells, NK cells and B cells are thought to play a role in the development of CAV since they are recruited in the inflamed cardiac allograft tissue. An ongoing project in the lab is aimed at characterizing the specificity and functioning of these infiltrating cells.

We hypothesized that the local effects mediating CAV would also result in systemic changes in the levels of different peripheral blood mononuclear cells (PBMCs). Consequently, we have begun the analysis of blood samples collected from heart transplant recipients during their annual biopsy. Thus far, we have collected samples from fifteen patients (mean year of collection±SD 3.4±1.5 years), three of whom had already been diagnosed with CAV (mean year of collection±SD 4±1). We also collected PBMCs from five healthy adult donors.

We used flow cytometry to assess the expression of twenty different cell surface markers to distinguish specific lymphocytic subsets and to identify any significant differences in lymphocytic populations between patients with CAV and those without. We found an overall increase in CD3+ lymphocytes (Mean±SD 4476±1172) for patients with CAV when compared to other heart transplant patients (2865±1120, p<0.05) In addition, CAV patients had higher naïve CD4+ cell counts (770±352), but lower late memory cell counts (4.8±2.0) when compared to other heart transplant patients (p<0.1). We also noted an increased percentage and number of activated CD4+CD28+CCR7+ (1955±966) and CD8+CD28+CCR7+ (632±430) memory cells (p<0.05), indicating memory cells might have an important role to play in the development of CAV and that the disease probably has a multifocal origin. However, we did not find statistically significant differences between different B cell subpopulations. These encouraging findings now require validation using additional PBMC samples from patients with and without CAV. In addition, the accuracy of the results will increase as additional data is collected over subsequent years and as the antibody panels are refined to focus on specific cells and surface markers.
Asthma is the primary reason for hospitalization of children in Boston, according to Children’s Hospital Boston. Asthma is especially of concern in Boston’s Chinatown, which is the third largest Chinese neighborhood in the country. Statistics from the Boston Public Health Commission’s 2009 Health of Boston Report showed that the prevalence of asthma in Boston’s Chinatown is 13%, as compared to the 10% Boston average. Furthermore, another study found that approximately 16% of students at Josiah Quincy Elementary School (JQES) reported a previous diagnosis of asthma and an estimated additional 3% of all students were undiagnosed.

Boston Asthma Swim is an afterschool community health program that was founded by students from Harvard Medical School and Harvard School of Dental Medicine in 2002 to address the need for targeted asthma education at JQES. The program aims to serve elementary school-aged children diagnosed with asthma by promoting learning about the disease and healthy behavior. Each Friday afternoon during this past school year, Asthma Swim took place at Boston Chinatown Neighborhood Center (BCNC) at JQES between 3:15 and 5:00 in the afternoon. The program was divided into two components. First, participants meet in the school’s activity room for a 45 minute session to learn about respiratory physiology, asthma triggers, asthma management, and healthy nutrition and exercise habits through fun, engaging games. The volunteers measured and recorded students’ peak exhalation flow rates, a marker of airway health. Afterwards, the program moved to the BCNC pool, and participants were divided into small groups based on ability and experience swimming. The purpose of the swimming was to promote general fitness, develops swimming skills, and stress water safety.

Evaluation of the program’s success was measured in many ways. First, participants underwent a preliminary evaluation of asthma knowledge and swimming ability at the beginning of the year. This will be repeated at the end of the year in December, and we hope to see an improvement in both knowledge of asthma management and advancement in swimming ability in each child. Throughout the year, we also sought feedback from program participants, parents, volunteers, and community partners regarding the quality of the classroom curriculum and swimming instruction.

Asthma Swim has been successful as the longest continually running program of its kind in Boston, thanks to its strong foundation and the hard work of past leaders, volunteers, and community partners, and we hope to continue to make improvements in the future.
Exploring the Relationship between Developmental Assets and Food Insecurity in Adolescents from a Low-income Community

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Background: Positive Youth Development (PYD) is a resiliency model rooted in the developmental assets framework that builds youths’ assets to help them overcome risks and create positive change in their lives and communities. Food insecurity is an important public health problem facing many low income communities. Whether food insecurity is associated with fewer developmental assets among adolescents is unknown.

Methods: Using a census approach, 2,516 middle and high school students from a low income, predominately minority urban Northeast community completed a survey that included the Development Assets Profile (DAP), Adolescent-Core Food Security Module (A-CSFM) and demographic questions. 2,350 students (48.2% male, 31.4% white, 3.7% black, 41.9 Hispanic, 5.1% Asian, 12.3% Other) submitted usable surveys. The DAP, a validated instrument with possible range 0-60, was scored using the total scale and context subscales (community, family, personal, school, social). Multivariable logistic regression analyses determined independent associations between developmental assets and food security adjusting for demographics.

Results: Mean DAP=38.9, IQR=14. 76.5% were food secure (FS), 14.9% had low food security (LFS) and 8.6% had very low food security (VLFS). Logistic regression comparing FS to LFS students and FS to VLFS student revealed higher total DAP score was associated with lower risk of food insecurity (OR$_{LFS}$=.97, 95% CI=.96-.98; OR$_{VLFS}$=.94, 95% CI=.92-.95), as was white race/ethnicity (OR$_{LFS}$=.67, 95% CI=.94-.99; OR$_{VLFS}$=.60, 95% CI=.43-.89). The DAP associations were driven by the family context subscale (OR$_{LFS}$=.96, 95% CI=.94-.99; OR$_{VLFS}$=.88, 95% CI=.86-.91) for both LFS and VLFS. For VLFS, higher community context scores were also associated with increased risk of food insecurity (OR=1.1, 95% CI=1.0-1.1).

Conclusions: White race/ethnicity and greater developmental assets, particularly family assets, were associated with reduced risk of food insecurity. Why higher community assets were also associated with increased odds of VLFS remains unclear and requires further research.
Search for the Mechanism of Resistance of HER2-positive Breast Cancer Brain Metastases to Targeted Therapies

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Breast cancer is the second most common cause of brain metastases. Human epidermal growth factor receptor 2 (HER2)-positive breast cancer patients are at a high risk of developing brain metastases, with a frequency as high as 50% in patients with advanced disease. The HER2 oncogene is amplified in approximately 25% of human breast cancers and, with advanced treatments and improved imaging, the incidence of brain metastases has been increasing.

While the anti-HER2 therapies trastuzumab and lapatinib have been shown to effectively control primary tumor growth and extra-cranial metastases in many patients, they have not been able to contain the growth of their associated brain metastases. Our laboratory aims to elucidate the mechanism of resistance of HER2-driven breast cancer brain metastases by testing several hypotheses.

To test whether growing in the brain microenvironment confers permanent resistance upon BT474 HER2-driven breast cancer cells, BT474 cells were directly injected into the brain parenchyma, allowed to form a brain lesion, and tumor tissue collected, and cells dissociated—the resulting cell line was named BT474-BR. Dose-response curves were generated for both cell lines after treatment with lapatinib and, because most HER2-driven breast cancers rely on the PI3K-Akt pathway, the PI3K inhibitor BKM120, in vitro. Both were found to be similarly responsive, suggesting that tumor cells rely on continuous stimuli from the brain microenvironment to remain resistant.

In order to determine whether inhibiting phosphoinositide-3-kinase (PI3K), a signaling molecule just downstream of HER2, would have a therapeutic affect on HER2-driven breast cancer brain metastases, nude mice were injected intracranially with ZR-75-30 cells, allowed to reach a specific tumor size, and treated with BKM120. Tumor size was estimated by measuring the blood luciferase activity in each mouse, as the tumor cells were engineered to express a secreted luciferase. Tumor size and survival was compared to nude mice with ZR-75-30 cells growing in the mammary fat pad (MFP). Both groups were compared to untreated controls. While BKM120 controlled tumor growth in the MFP after 30 days, it did not affect intracranial tumor growth.

Previous studies have shown that contact with astrocytes upregulates survival genes and may protect tumor cells from chemotherapy. To determine whether contact with astrocytes causes BT474 HER2-driven breast cancer cells to develop resistance to HER2 and PI3K inhibitors, we were developing a co-culture model that can be used with cleaved caspase-3 staining to visualize differential apoptotic responses to treatment. Other apoptotic markers and the optimal time and dose are being determined.
Comparison of Breast Reconstruction Outcomes
With and Without the Use of Acellular Dermal Matrix

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Breast cancer is the most common cancer in women. In 2011, according to the American Society of Plastic surgeon, over 96,000 women underwent breast reconstruction following mastectomy. 79% were immediate or delayed tissue expander-implant or implant based breast reconstructions. In recent years, reconstructive surgeons have begun to incorporate acellular dermal matrices (ADMs) in such reconstructions to improve aesthetic outcomes by creating the inferolateral portion of the expander pocket, thereby constructing a more natural appearing breast. An ADM is a bio-prosthetic material produced from human cadaveric or animal sources that creates a tissue conductive biological scaffold, which is slowly revascularized and remodeled into autologous tissue following implantation.

While ADM use is increasingly more popular among plastic surgeons it is unclear whether it increases post-operative complication rates. Previous studies were single-institution, included a few hundred patients and yielded inconclusive results. As such, we conducted the first controlled evaluation of acellular dermal matrix use as compared to traditional reconstruction techniques in a large patient population, using a multi-institutional database. We aimed to determine whether postoperative complication rates vary between patients who did and did not receive acellular dermal matrices. Additionally we aimed to determine whether certain preoperative demographics and/or comorbidities affect complication rates.

To do so we used the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database, which utilizes a dedicated Surgical Clinical Reviewer at each participating institution to input standardized surgical data into this national database. We extracted pertinent data to breast reconstruction cases using Current Procedural Terminology codes and recoded it into binary form for ease of analysis. Differences in complication rates (list) were analyzed using Chi-square analysis in SPSS. We ran multivariate analyses in SAS to determine whether demographics and comorbidities affected outcomes.

Out of 1042 cases, 118 had acellular dermal matrix implants. There were no statistically significant differences found in complication rates, including but not limited to: superficial surgical site infection, deep incisional SSI, wound disruption, pulmonary embolism etc. Up to date multivariate analysis indicates that none of our comorbidities serve as predictors for complication rates among breast reconstruction patients but analyses still need to be run on each subgroup: ADM and non ADM.

Thus far, our data suggests ADM use is safe in breast reconstruction patients undergoing implant-based reconstruction. The incidence of complication rates is not increased. Further analysis will reveal whether a particular method is more suitable for specific subsections of the population.
Auditory brainstem implants (ABIs) help provide some hearing to patients with non-functional auditory nerves or ossified cochleae. Yet, performance of ABI users in speech reception tasks is usually worse than for cochlear implant users. ABIs bypass the cochlea and auditory nerve and electrically stimulate the surface of the cochlear nuclear complex. Two of the possible reasons for their limited performance are: (1) the relative imprecision of device placement, making it difficult to specifically target frequency regions important for speech understanding, and (2) poor spatial selectivity of electrical stimulation that limits frequency resolution.

To quantify the spatial selectivity of electrical stimulation, we stimulated the surface of the cochlear nucleus (CN) of anesthetized rats while recording multiunit activity in the contralateral inferior colliculus (IC) with a multichannel micro-electrode array. Consistent with the tonotopic organization of the dorsal CN and IC, we found that CN surface stimulation laterally (low frequencies) to medially (high frequencies) led to lower activation thresholds dorsally to ventrally in the IC, suggesting that some frequency information is preserved with electrical stimulation. Yet, spatial selectivity of electrical stimulation was usually poor, as stimulation in one point of the CN led to activation of most of the tonotopic axis in the IC.

These results point to the need for improved electrode design and new stimulation strategies to improve frequency representation in the central auditory system of ABI users. An optogenetic approach may be promising in this regard, as light may be more easily focused than electrical current. To test the feasibility of optogenetic control of the auditory brainstem, we transfected the CN of CBA/J mice with AAV2/8-Channelrhodopsin-2 (ChR2). Following an incubation period of two to four weeks, we stimulated the surface of the CN with blue light while recording neural activity in the contralateral IC. We found a significant increase in IC activity during blue light stimulation in mice with ChR2 expression in the CN. In contrast, no significant increase in neural firing was seen in the IC in mice with ChR2 expression outside the CN or in non-transfected control mice.

Overall, these results demonstrate the feasibility of optogenetic control of the auditory brainstem and may lay the groundwork for a new generation opto-electronic ABI.
Let’s Talk About Gender: 
Exploring a Sexual Health Education Context for Sexual Violence Prevention

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Sexual violence (SV) affects at least one in six people, most often before age 25. While the surgeon general’s broad definition of sexual health now references this reality, sexual health education (sex-ed) has not expanded its scope. This project explored the integration of SV prevention and sex-ed in service of an existing program known as Prevention, Health Awareness, and Choice through Education (PHACE). PHACE consists of ten, weekly, one-hour sessions run by Harvard Medical School students at two of Boston’s public McKinley schools, which serve students needing extensive social, emotional, and academic support. I planned to draft an integrated curriculum synthesizing the approaches of sex-ed and SV prevention. I anticipated complex challenges addressing SV in a community where it is prevalent (as reported anecdotally by McKinley school educators); any curriculum suggestions would serve only as a basis for future planning around this issue within the school community.

A literature analysis identified gender role rigidity and adherence as an area of potentially productive overlap between SV prevention and sex-ed, and led me to a rubric for addressing SV within a community affected by childhood sexual abuse. Through interviews and referrals I found Gender Matters (Gen.M), a new project run by international health organization EngenderHealth and Austin, TX-based sexual/domestic violence resource center Safe Place. With Department of Health and Human Services funding, Gen.M is evaluating an intervention focusing on gender-based attitudes and behaviors - drawn from Safe Place’s expertise in SV awareness and prevention - to prevent teen pregnancy. Gen.M’s gender transformative approach is poised to assess the possible benefits of organizing sex-ed around a critical analysis of gender norms, exactly the area of overlap I had identified through my literature analysis. I discussed my project’s goals with the Gen.M’s coordinator, and obtained a draft copy of their curriculum in advance of implementation in July 2012. With EngenderHealth’s approval, I reframed my curriculum development goal in terms of exploring an adaptation Gen.M to PHACE’s framework.

McKinley staff responded positively to Gen.M’s approach to sex-ed through identity and relationships, and were eager to see PHACE incorporate Gen.M’s interactive elements. They felt employing strategies heretofore used only in SV prevention to teach sex-ed was an appropriate first step toward addressing SV in their community. Thus, I recommend PHACE consider adapting Gen.M’s gender transformative approach in service of McKinley school students’ complex rights to sexual health and freedom from committing or experiencing sexual violence.
Germline BRCA1 and BRCA2 mutations increase susceptibility to breast cancer. Despite similar functions as DNA repair proteins, mutations in these genes give rise to phenotypically distinct tumors. The majority of BRCA1-associated tumors have a basal-like, “triple-negative” (TNBC) phenotype: sporadic TNBC has been associated with a propensity for central nervous system (CNS) metastasis. Unlike BRCA1, BRCA2-associated tumors often overexpress hormone receptors. Limited information is available on CNS metastasis among BRCA2 carriers with breast cancer. Because treatments differ in their ability to penetrate the CNS, treatment decisions might be affected if BRCA1/2 mutations increase risk for CNS metastasis. Furthermore, CNS metastases can be subgrouped into parenchymal and leptomeningeal metastases. To our best knowledge, risk of leptomeningeal carcinomatosis (LC) among BRCA1/2 carriers has not been described. The purpose of this study was to characterize the pattern of CNS metastasis among breast cancer patients who are BRCA1/2 carriers and compare to noncarriers.

Thirty-one BRCA1 carriers, 31 BRCA2 carriers, and 169 noncarriers were included in a retrospective cohort study. Patients were identified among women diagnosed with Stage I-IV breast cancer who received treatment at Dana-Farber Cancer Institute and have been tested for BRCA1/2 mutations. All women have had at least one cancer recurrence event or presented initially with Stage IV disease.

BRCA1 carriers were younger at presentation (p=0.03) and were more likely to have TNBC (55% vs 25%, p=0.001) than noncarriers. Among TNBC patients, BRCA1 carriers were more likely than noncarriers to have parenchymal metastasis (21% vs 5%, p=0.04) and LC (11% vs 0%, p=0.03) as the first recurrence event. When all events were analyzed, rate of parenchymal metastasis was not significantly increased among BRCA1 carriers compared to noncarriers (47% vs 34%, p=0.32), but rate of LC was significantly increased (37% vs 2%, p<0.001). BRCA2 carriers were not significantly younger at presentation than noncarriers (p=0.28), but more often had ER-positive breast cancer (81% vs. 59%, p=0.02). Among ER-positive breast cancer patients, BRCA2 carriers similar rate of parenchymal metastasis as noncarriers for first event (3% vs. 4%, p=0.81) and overall (35% vs. 25%, p=0.22). However, LC occurred more frequently overall among BRCA2 carriers than noncarriers (23% vs. 7%, p=0.004), though it was usually not a first event in either cohort. These data suggest that BRCA1/2 mutations are associated with distinct CNS metastasis patterns.

Analysis is still ongoing; final data will be presented at Soma Weiss Day.
Examining the Effects of Learning a 3-D Spatial Memory Task on Dreaming

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Researchers have long debated which factors govern why some daily experiences emerge in dreams while others do not. Previous work in our laboratory suggests that salience of the learning task mediated by added factors such as reward and auditory feedback increase dreaming. We seek to determine which of these factor(s) were the principle effectors of increased dreaming and learning.

Participants (n=80) were broken down into four groups. One group was trained on a version of the maze with no added manipulations (neither), one with only the audio feedback (feedback), one with only the reward (reward), and the last with both (both). Participants explored the maze and then were tested across 3 trials. After completion, they spent the night in the laboratory with EEG monitoring. Dream reports were collected at 13 points during sleep and retesting of the maze was administered within an hour of waking.

Improvement in time to complete the maze was most markedly seen in the feedback group (16.9% improvement overnight), followed by the neither group (11.9%), the both group (1.8%), and lastly the reward group (-27.0%). The both group (7.41%) showed the greatest proportion of maze related dreaming, followed by the reward (6.17%) and feedback (6.00%) groups, and finally the neither (2.52%) group.

The dreaming data is consistent with our prediction that the feedback, reward, and both groups would have more maze related mentation during sleep than the neither group. Surprisingly, this increased mentation does not appear to translate to increased learning. In fact, the feedback group learned the task most successfully, the reward group actually got worse overnight, and the both group appeared to approximate a summation of these effects.

We speculate that both feedback and reward increased incorporation of the task into dreaming by enhancing the general salience of the task, via difference mechanisms. However, while the feedback condition seems to augment learning, the reward condition appears destructive to learning. We hypothesize that this may be due to the anxiety and stress-inducing qualities of the reward manipulation as compared to the calming and helpful qualities of the audio feedback. Future studies would aim to employ cortisol analysis to determine if this effect is truly stress related.

Thus, our data suggests that the salience of a new learning task mediates incorporation into dreaming and potentially learning of the task, and that stress may dampen or reverse the effect of these learning benefits.
Relative Bradycardia with Hypertension in Traumatic Brain Injury: A Marker for Mortality?

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Traumatic brain injury (TBI) is a leading cause of death in patients under 45 years of age. Hypertension has been shown to be associated with increased mortality in patients with moderate to severe traumatic brain injury (TBI). Furthermore, it is known that relative bradycardia is associated with increased mortality in hypotensive patients. We conducted a study to evaluate the relationship of initial heart rate (HR) with outcome in hypertensive TBI patients.

This was a retrospective study of adult patients with moderate to severe blunt TBI (GCS ≤13) that presented to a Level I trauma center (2001-2011). Patients with hypertension, defined as an initial emergency department systolic blood pressure (SBP) ≥140 mmHg, were included in the analysis. The primary outcome was in-hospital mortality. Logistic regression analysis was used to control for age, injury severity, midline shift >5mm, pupil reflexes, hyperosmolar therapy, and blood transfusion. Secondary outcomes, including GOS scores, were also analyzed.

Of 490 patients with moderate to severe TBI, 53 patients were excluded. Of the remaining 437 patients, 223 (51%) presented with hypertension. Total in-hospital mortality was 31% in this group and the initial HR was significantly lower in the group that died (86±26 vs. 96±23; p=0.009). Bradycardia (HR≤60) upon presentation, which was identified in 21 (9%) patients, was associated with increased mortality (71% in HR≤60 vs. 27% in HR>60; p<0.001). Logistic regression identified bradycardia as an independent predictor of mortality (odds ratio 4.82; 95% confidence interval 1.36-17.10; p=0.015). Further subgroup analysis of relative bradycardia failed to identify HR between 60 and 90 as a predictor of mortality (p=0.113), although HR≤60 remained significant (p=0.006).

The combination of initial hypertension and bradycardia in moderate to severe blunt TBI patients is associated with increased mortality.
Impact of Obesity on Postoperative Morbidity and Mortality in the Surgical Patient at Faulkner Hospital

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Background: Obesity is a multifactorial disease that affects approximately 97 million adults in the United States. It is considered a risk factor for postoperative morbidity and mortality (M&M), including surgical site infections (SSI). Annually, SSIs make up 37% of all hospital-acquired infections. However, the exact impact of obesity on such complications has yet to be sufficiently characterized. Body mass index (BMI) is the most common way to measure obesity. Standardized risk assessment models use BMI to predict postoperative complications. Though easy to use, BMI cannot distinguish between fat and non-fat tissues. In contrast, percent body fat, measured by bioelectrical impedance analysis (BIA) characterizes the patients’ adiposity. BIA analyzes body composition, differentiating between fat tissue, water, and skeletal tissue.

Hypothesis: Because we are interested in how fat influences surgical outcome, we hypothesize that percent body fat is a more accurate metric of obesity and better predictor of risk when incorporated into current risk assessment models.

Methods: To test this hypothesis, a prospective cohort of adults undergoing elective surgery at Faulkner Hospital in Boston was studied (n=222). Patients who met inclusion criteria were followed through 90 days after their elective surgery. Percent body fat measurements were obtained at participants’ preoperative screening visits using BIA technology. Preoperative and postoperative data were collected by reviewing subjects’ medical records. In order to achieve 80% power, we estimated our sample size to be 456 subjects.

Results: Given our 90-day follow-up, we have collected data on half of our patients to date (n=222). All classifications are based on the most current CDC definitions. 90-day follow-up data reveal a total complication rate of 10.8%, with 25 patients experiencing post-operative complications. With BMI defining obesity, postoperative complication rate was 15.5% in obese patients and 7.8% in non-obese patients. Using percent body fat, complications occurred in 12.3% of our obese patients and 2.9% in our non-obese patients.

Discussion: Our preliminary data demonstrate that a higher complication rate is observed among obese patients when percent body fat captures patients’ obesity. This suggests that percent body fat is a better predictor of risk because it captures more individuals as obese. Data collection will continue until we have reached our target sample size. Following completion of data collection, we will use multivariable regression analysis for binary and continuous outcomes and assess interaction effects among significant variables.
Role of FGF2/9 in the growing cranial base synchondrosis

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Craniosynostosis is a premature fusion of the cranial sutures, which are joints that consist of fibrous tissues and mesenchyme connecting adjacent flat bones of the skull. Fusion of cranial flat bones via these joints needs to occur at specific time and location during cranial development. Defects in this pathway lead to deformities of cranial features.

Fibrous growth factors (FGFs) and fibrous growth factor receptors (FGFRs) have been shown to be essential in the vertebral skeletal development. Mutations in FGFR2, for example, have been studied in context of various syndromic craniosynostoses. In addition, FGF9 has been found to be another critical factor for skeletal development. Some clinical reports and experiments with FGFR2 knock-in models implicate the possible role of FGF/FGFRs in the regulation of chondrogenesis. Based on the previous studies, we hypothesized that FGF2/9 signaling is involved in the growing cranial base synchondrosis, especially affecting the chondrocyte differentiation and proliferation stages.

Parasagittal sections (5μm) from the spheno-occipital synchondrosis of postnatal day 1 (P1), P2, P3, P5, and P7 mice were prepared via paraffin embedding and microtome sectioning. The specimens were stained with Hematoxylin and Eosin (H&E) for histologic observation. Immunohistochemistry was performed by applying polyclonal anti-rabbit antibodies specific for FGF2 and FGF9. Length, width, and area of related structures in the spheno-occipital synchondrosis were studied via morphometric analysis.

As hypothesized, both FGF2 and FGF9 were involved in the growing cranial base. The FGF2 expression was both ubiquitous and unspecific; it was found in all three zones (resting, proliferating, and hypertrophic) of the spheno-occipital synchondrosis. In contrast, the FGF9 expression was localized and specific; it was only found in the transmitting zone. However, both FGF2 and FGF9 expressions were present in the spheno-occipital synchondrosis of all postnatal mice tested (P1, P2, P3, P5, and P7).

These patterns of FGF expressions suggest that while both FGF2 and FGF9 are involved in osteogenesis, they regulate cartilage differentiation at different stages. The ubiquitous expression of FGF2 in all three zones implies that FGF2 may be a regulator either at all stages of osteogenesis or at earlier stages. In contrast, localized FGF9 expression in the transmitting zone indicates that FGF9 controls for osteogenesis, specifically at later stages. This study suggests the role of FGF2/9 in the growing cranial base synchondrosis of mice up to P7. Further experiments involving older mice may help to clarify the role of FGF2/9 in later stages of cranial development.
Surgibox: Prototyping a Device to Regulate Intra-Operative Conditions at a Surgical Site

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Surgery is increasingly important in global health, but safe surgery remains a challenge in austere settings. Patients in these settings are often highly vulnerable to severe infectious complications due to HIV, malnutrition, comorbidities, advanced disease, multidrug resistance, etc – up to 10x as vulnerable, according to data from a Ugandan obstetric clinic. This is exacerbated by patients’ exposure to airborne contaminants during surgeries in bare rooms, tents, or even open spaces, where viscera are vulnerable to pathogens, particulate matter, inappropriate humidity, temperature extremes, and insects.

Several modalities have been proposed or implemented to address this issue. These include surgical tents, laminar-flow ventilation systems, disinfectant sprays, and wound care protocols. However, these solutions are prohibitively costly, difficult to implement and maintain, and inconsistent. This project’s purpose is to design a device that literally shrinks the problem scope from controlling air in an entire room, to <1/10 of a cubic meter around the incision. The solution concept: a series of connected, sterile-interior containers covering a surgical site, accessed through arm and material ports.

The project’s purpose is to 1) assess feasibility, 2) optimize design, 3) fabricate prototypes for animal and field testing. During the SMO summer 2012 fellowship, I completed steps 1 and 2. Specific aims included: optimize device shape, size, and structure; determine appropriate interfaces for operator access to the controlled field; and study materials.

Based on anthropometric data, the device was designed for torso sizes in the 5-95% range, suitable for common thoracic, abdominal, and obstetric procedures. The device is comprised of separable units in addition to an instrument tray that may be recombined based on the surgical need. Sealable armholes were added to accommodate 1-2 surgeons and 1-2 assistants, permitting additional operators and surgeries on either side of midline as needed. Side ports were added for introduction and removal of materials and a rostral port was added for neonate delivery via Caesarian section.

Optimization occurred through computer aided design, followed by iterative prototyping. Frame configuration was tested via full-size models built from plastic straws and, later, wooden dowels fitted to blocks. Ports were tested in foam-and-vinyl models. Materials were assessed for chemical and heat sterilizability (data tables), durability, and ease of use.

The result is two candidate designs with complete sets of design optimization data. Ongoing research will choose the final design, based on durability, portability, effectiveness, and ease of operator use; prototype fabrication is pending.
Investigation of Wnt signaling and the apoptotic response to acute injury in dental tissue repair

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Background: Oral trauma, though usually not life-threatening, is both a common and serious clinical problem. Injury to dental tissue and the surrounding oral environment is typically associated with issues in pain, mastication, alimentation, and speech. Consequently, it is of clinical importance to investigate the mechanism of natural tissue repair as a means to preserve tooth functionality in patients with oral trauma. Induction of the canonical Wnt signaling pathway has been identified as an early response to tissue damage. Recent studies have also pointed to the role of apoptotic cells as a necessary and sufficient source of Wnt-based regeneration in the hydra model, but little is known of the contribution of programmed cell death to tissue repair in other organisms.

Objectives: To explore whether cells undergo apoptosis in response to dental trauma, we induced damage in murine incisors and assayed for in situ cell death. In order to investigate the temporal effect on Wnt-mediated dental tissue repair, we observed the cellular response over time to post-eruption damage in the incisors of Axin2\textsuperscript{LacZ} reporter mice.

Methods: Dental trauma was induced via submandibular hypodermic needle in CD1 wild-type mice (7 days post-natal), which were collected at 1h, 2h, 4h, and 8h time points post-damage. After tissue fixation and cryosectioning, apoptotic cells were labeled via the terminal deoxyribonucleotidyl transferase dUTP nick end labeling (TUNEL) assay and analyzed using confocal microscopy. To assess Wnt activity as a function of time, the incisors of Axin2\textsuperscript{LacZ} reporter mice were clipped after eruption (12 days post-natal) and mandibles were harvested 1 day, 1 week and 2 weeks post-damage for fixation and cryosectioning. The tissue sections were stained for LacZ expression with β-galactosidase and analyzed via bright field microscopy.

Results: Populations of TUNEL-positive cells were present across all four collection points with progressively fewer observable apoptotic cells over time. Moreover, these TUNEL-positive cells were localized around sites of damage in tissue sections where needle entry was discernible. Positive LacZ staining was observed through the 1-week post-damage time point in the tissues peripheral to the dental pulp and cervical loop of Axin2\textsuperscript{LacZ} mandibles.

Discussion: The presence of apoptotic cells near sites of damage suggests that programmed cell death may play a key role in mediating tissue repair. Further studies correlating apoptosis with the induction of Wnt activity may elucidate the preliminary response to acute dental trauma.
Strengthening Monitoring and Evaluation: A survey and comparative analysis of current mobile health technology pilots

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In 2010 eight global health agencies, including GAVI, agreed that information and communication technology (ICT) is central to improving, utilizing, and monitoring programs for results in efforts to meet the Millennium Development Goals (MDG). This meeting led to investments from global health leaders, including WHO, PATH, and the Gates Foundation, in electronic and mobile health. Thereafter, the use of mobile devices in healthcare (mHealth) has grown rapidly throughout the developing world revolutionizing the delivery of healthcare, both in urban slums and to the most remote “last mile” patients. Through electronic data entry and transmission, mHealth provides real-time data collection and reporting from the initial source while eliminating error-introducing manual data transfers.

While the WHO has collected incidence data on mHealth pilots, comprehensive descriptions are rarely available. This study developed characteristics to describe and compare mHealth pilots, specifically considering data architecture and pilot sustainability. A survey of peer reviewed literature, mHealth databases, and Google produced a list of eligible pilots, which were systematically described accordingly in a customized database. Information about each pilot was found on pilot and partner websites, in press statements or lay media, or within an organization’s blog; no information was available in peer-reviewed literature.

By highlighting trends in the data collected and strong example pilots, the final report to GAVI serves as a framework for understanding proposed or existing mHealth pilots and includes a draft evaluation guide. This report focuses on five aspects of mHealth pilots determined to be the foundation of success, including: selection of technology, process of data entry and reporting, degree of interoperability, sustainability of design, and use of rigorous monitoring and evaluation. With this snapshot of mHealth, GAVI is enabled to leverage its influence in shaping or catalyzing the future of mHealth in immunization.

This study directly addresses GAVI’s need to understand mHealth as it is being used in GAVI eligible countries. Importantly, the design of this project and the information collected are innovative in the field of mHealth as the data used for comparison has not been available in any single database to this point. The final report presents a list of characteristics developed to describe and compare mHealth pilots, including the health priority met, indicators measured, data architecture selected, and evaluations conducted.
Changing the Way We Approach Medically Complex Children: A Screener for Unmet Needs

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Medically complex children have at least one chronic condition resulting in high service needs, including medication, equipment and multiple subspecialist involvement. Evidence has shown that increased care coordination reduces the number and length of hospital stays, and decreases healthcare costs.

The Rainbow Medical Home Initiative (RMHI) at Children’s Hospital Primary Care Center targets the medical and social care coordination needs of this population. In 2011, 91.3% of caretakers reported unmet needs in at least one of the following areas: medical equipment, medical supplies, educational and therapy services, mental health support, recreational/social opportunities and home caregiver support. 47.1% reported unmet needs in 3 or more areas. The objectives of this project are: 1) develop a screener for unmet needs amongst RMHI families; and 2) assess the acceptability and feasibility of incorporating this screener into routine care. If successful, this screener will allow providers to more proactively address patients’ unmet needs.

Two focus groups and 4 cognitive interviews of families were performed to evaluate the completeness, format and literacy level of a draft of the screener. The screener was piloted during the summer of 2012 at patient visits. Feedback on the acceptability and feasibility of screener implementation was solicited through surveys from stakeholders (patient families, providers, social work and administrative staff). Qualitative feedback was solicited in group format from stakeholders to elicit process issues not accounted for by our surveys. Feedback was incorporated into a more refined screener that was distributed during the second half of summer. A similar feedback cycle was performed to develop the final screener.

Major unmet needs identified by the 70 completed screeners are: securing educational services (12/25, 48%), finding people or programs parents can trust to help care for their child (22/68, 32%) and finding recreational/social opportunities (21/69, 30%). The 62 stakeholders queried generally agree that the screener helps identify needs and improves communication between providers and families. Most stakeholders believe that the screener is feasible to incorporate into routine practice.

This project will improve the effectiveness and efficiency of our Medical Home by enhancing our understanding of our patients’ non-medical issues. Future directions include screener incorporation into routine practice; screener translation into Spanish; ongoing data collection of unmet needs; development of resources to respond to these needs; dissemination of results to clinical care teams and training on resources designed to address them. Lastly, we will be tracking patient utilization of Social Work pre- and post-screener implementation.
Operation Mouthguard

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Operation Mouthguard (OM) is a community service project, run by students of the Harvard School of Dental Medicine since 2002. OM’s goals have continued to evolve as it addresses the needs of the local community of children. The goals include 1) To provide custom-made mouthguards to low-income high school sports teams of the Boston Area 2) To promote oral health awareness and safety among children of the community via the educational component. This entails workshops on oral hygiene, trauma prevention and on oral effects of alcohol and tobacco. These goals contribute to helping the children we serve by increasing the quality and years of healthy life, and to eliminating health disparities that may include differences that occur by race or ethnicity, education or income, gender, and urban locality.

Custom-fitted mouthguards supplied by OM are valued at or over $100, and are superior to traditional ‘boil and bite’ or ‘stock’ mouthguards that are usually purchased at sporting goods stores. Custom-fitted mouthguards fit more tightly and evenly, and provide better protection and comfort. OM realizes that many children in the Boston area from low-income households are likely to be deprived of such protection due to expenses. We will be able to reach these children by partnering with the Boys and Girls Clubs of Boston, local high schools, and the MGH Healthcare Center.

OM is run on an event basis, and each event involves two sessions: the first at the community center site, and the second at the dental school student laboratory. The first session requires at least 10 students for 2 hours. At this time, third and fourth year HSDM students take impressions of children’s teeth under supervision of a faculty member, while first and second year HSDM students provide oral health education. The second session requires at least 15 students for 3 hours. At this time, HSDM students use the impression and equipments to make properly fitted mouthguards. The oral health education piece of OM is a brief interactive session involving 2-3 HSDM students and 6-7 children. Children learn about the importance of wearing mouthguards, brushing and flossing, dental anatomy and tobacco’s effects on the body and oral cavity. Hands-on demonstrations are also in preparation to teach participants about the beneficial effects of fluoride, the detrimental effects of soda and other acidic foods on teeth. Our goal is to make children aware of oral health issues and what they can do to improve their own oral health.
Medication switch in post-MI patients following elimination of out-of-pocket costs

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Medication non-adherence is a major public health problem, costing 125,000 lives and between $100 billion and $300 billion annually. Numerous studies have shown an inverse relationship between patient cost-sharing (i.e. copayments) and adherence to essential therapies and between adherence to medications and the risk of subsequent hospitalization and health care spending. In response, insurance companies and other health care payers have reevaluated the merits of patient cost-sharing that are purely based on the cost of drugs and are have shifted towards value based insurance designs, which ties patient cost-sharing to the clinical value of treatments. For therapies of high clinical value, this has generally meant substantially reducing or eliminating medication copayments altogether. However, reducing copayments might create incentives for patients who are using less expensive generic medications to switch to therapeutically equivalent but more expensive brand name medications in the same drug class.

To analyze the impact of patient cost-sharing on medication switching, we conducted a secondary analysis of the MI FREEE trial, which investigated the impact of eliminating patient cost-sharing on adherence to three classes of standard-of-care medications among patients discharged after myocardial infarction (MI) - statins, beta-blockers, and angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB). The trial found that patients randomly assigned to receive full coverage of the medications (study group) had statistically better adherence, and reductions in rates of major vascular events, but no significant differences in the primary clinical outcomes (major vascular events or revascularization) compared to those in the standard coverage group (control).

For patients who filled medications after hospital discharge, 174 switched statins [77 (44%) control, 97 (56%) study], 249 switched beta-blockers [120 (48%) control, 129 (52%) study], and 133 switched ACEI/ARB [59 (44%) control, 74 (56%) study] within 90 days of randomization into the study. Looking specifically at generic-to-brand switches, there were 64 switches for statins [23 (36%) control, 41 (64%) study group], 32 for beta blockers [10 (31%) control, 22 (69%) study group], and 55 for ACEI/ARB [23 (42%) control, 32 (58%) study group]. On this basis, we conclude that patients who incur no out-of-pocket cost for their post-MI medications are more likely to switch from generic to brand drugs than are patients in the standard coverage group. This finding may impact the economic implications of this quality improvement strategy. We are currently conducting statistical analyses to determine the significance of these switch differences as well as their impact on costs.
Pre-operative Hyperglycemia as Predictor of Adverse Post-operative Outcomes in Patients without Diabetes

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Although diabetes mellitus significantly influences post-operative outcomes, the implications of unrecognized pre-operative hyperglycemia are not clearly understood. We investigated whether pre-operative glucose can be useful to predict post-operative outcomes in non-diabetic patients.

We obtained information from the National Surgical Quality Improvement Program Brigham and Women’s Hospital (NSQIP BWH) database for 9758 patients who underwent non-emergent vascular and general surgery at BWH from 1/1/2005 through 4/5/2010. We used last glucose measured within 30 days prior to surgery as the primary independent variable. The primary outcome was any post-operative infection within 30 days. Analyses were performed using student’s t-test and logistic regression in STATA 12.

The post-operative infection rates for non-diabetic patients with pre-operative glucose <70 mg/dl, 70-100 mg/dl, 100-140 mg/dl, 140-180 mg/dl, and >180 mg/dl were 5.3%, 5.8%, 9.0%, 10.2%, and 6.3% respectively, showing an increasing then decreasing trend. Patients above 100 mg/dl had higher infection rates (9.1% vs. 5.7%; p<0.0001) than those with lower glucose levels (OR=1.6 (1.35-1.99)). Patients with pre-operative glucose >180 mg/dl had a decrease in glucose post-operatively (3-day post-operative mean 51.3 mg/dl lower than the pre-operative level) whereas those with pre-operative glucose <180 mg/dl had an increase (23.8 mg/dl higher; p<0.0001).

Mild pre-operative hyperglycemia (i.e. >100 mg/dl) in non-diabetic patients is a significant marker for post-operative infections. The drop in infection rates in the group with pre-operative glucose >180 mg/dl possibly reflects recognition and treatment of hyperglycemia, as suggested by our post-operative glucose data. Further studies are needed to determine whether screening and identification of hyperglycemia in non-diabetic patients would lead to improved post-operative outcomes.
Radical Cystectomy: Assessment of Perioperative Morbidity in Elderly Patients

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The existing scientific literature exploring the decision for radical cystectomy among elderly patients (greater than 70 years old) is not in agreement. Some studies report there to be a greater risk among elderly patients of suffering from perioperative complications and morbidity. However, several recent studies on radical cystectomy report acceptable complication rates among patients older than 70 years. Because of this controversy over advanced age and treating patients with radical cystectomy, a clinical recommendation regarding for this circumstance is currently missing. As a result, many clinicians are reluctant to recommend radical cystectomy in elderly patients with bladder cancer. Our project addresses this pertinent issue — especially in light of recent surgical technique advancements, improved intensive care treatment, and increased access to antibiotics, which have increased the potential for elderly patient survival with this surgery.

We conducted a retrospective observational study of 52 patients (≥70 years old) who underwent radical cystectomy for primary bladder cancer at the Brigham and Women’s Urology Department between 1995 and 2011. Co-morbidity information, length of stay, post-operative complications, date of tolerating house diet post-operation, BMI, ASA Score, and pre-operative GFR were obtained through a medical record review of each patient. Multivariate analysis is currently being conducted to determine what factors (as measured by the Charlson Co-morbidity Score, BMI, pre-operative GFR, ASA Score, and age at Cystectomy) had a significant correlation to perioperative outcome (as measured by length of stay, Clavien Postoperative Complication Score, and tolerating house diet before 7 days post-operation). Data analysis will be finished by the end of September.

A limitation of the study is that some patient medical files were found to be incomplete and missing co-morbidity data. Furthermore, some patients might have had co-morbidities that have yet to be diagnosed. Since it was not feasible to track down each patient and screen them individually, it was assumed that the co-morbidities reported were the only ones the patients had. Because of the small sample size of this study, follow-up studies with larger patient populations would help expand on the results.
Hematologic Profile in CLOVES Syndrome and Risk of Thromboembolism

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Congenital lipomatous overgrowth, vascular malformations, epidermal nevi and skeletal/scoliosis/spinal abnormalities (CLOVES) syndrome is a rare vascular overgrowth syndrome with significant venous thromboembolic (VTE) risk. It has been postulated that central and thoracic venous ectasia in patients with CLOVES contributes significantly to VTE risk. It is unknown whether hematologic factors also contribute to VTE risk in CLOVES patients, in addition to slow blood flow due to ectatic veins in vascular malformations. Our study aimed to characterize baseline coagulation profiles and the location and extent of venous ectasia in a large cohort of CLOVES patients and correlate these with VTE.

A retrospective review of medical records was performed including patients with CLOVES syndrome referred to the Vascular Anomalies Center from 1994-2012. Coagulation parameters at clinical baseline and the occurrence of venous thromboembolic events were collected. To minimize confounders of coagulation studies, baseline clinical status was defined as no recent illness, procedure or anticoagulation. Imaging studies were reviewed to characterize the location and severity of venous ectasia.

Of 79 patients with CLOVES syndrome, sufficient clinical data for analysis were found in 64. 12 VTEs occurred (18.8%), six of which were pulmonary embolism (9.4%). Of 25 patients with an available baseline platelet count, mild or borderline thrombocytopenia (<250K cells/µl) was noted in six patients, four of whom had VTE. Among 20 patients with baseline D-dimers, elevated D-dimer was noted in 12 patients, 3 of whom had VTE. The risk ratio of venous thromboembolism in patients with platelet count <250K cells/µl is 15.2 (95% CI: 2.15 to 107.6; p=0.006) and with elevated D-dimer is 1.00 (95% CI: 0.21-4.7; p=1.00). Prothrombin time, partial thromboplastin time and fibrinogen are often normal in CLOVES and do not predict VTE risk. Compared to patients without VTE, a higher percentage of patients with VTE had ectasia of the following veins: subclavian, axillary, basilic, marginal venous system of the trunk and lower extremity, and sciatic vein.

At clinical baseline, coagulopathy is rare and mild in CLOVES syndrome while phlebectasia is common and frequently severe. While venous ectasia may contribute to VTE risk, ectasia is common and does not predict VTE in patients with CLOVES. Low platelet counts are uncommon in CLOVES and may be secondary to venous stasis, but are statistically associated with VTE. Future work will study the utility of thrombocytopenia as a predictor of VTE, the effectiveness of anticoagulation and/or vena caval filters peri-procedurally to reduce risk of VTE, as well as the utility of closure of ectatic veins early in life.
Bronchial artery embolization for hemoptysis: Analysis of a 14-year clinical experience

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**Background**: Life-threatening hemoptysis can present in patients with a variety of underlying conditions, requiring an integrated treatment approach. We sought to describe and analyze our clinical experience with bronchial artery embolization (BAE) in patients with hemoptysis.

**Methods**: A retrospective review was performed, capturing 82 patients presenting with hemoptysis and undergoing BAE from 1998 to 2011.

**Results**: Men and women were equally likely to present with hemoptysis. The most common etiologies requiring BAE were malignancy (24/82) and cystic fibrosis (20/82). Patients with arteriovenous malformation (odds ratio Infinity, p=0.04) and aspergilloma (odds ratio 8.93, p=0.02) were more likely to also require embolization of systemic vessels. Alternatively, cystic fibrosis was associated with embolization of only the bronchial artery (odds ratio 0, p=0.07). The most common sites of bleeding were the right (68.3%) and upper lungs (RUL 31.7%, LUL 18.3%). After BAE, the following percent of patients were free of bleeding in these time periods: (76.8%, 0-48h); (79.5%, 2-7d); (93.9%, 7-30d); (82.3%, 30-180d); and (74.1%, 180-360d). Due to hemoptysis recurrence, 22.0% required re-embolization and 4.88% required surgery. As compared with 1998-2004, patients receiving BAE in 2005-2011 experienced better outcomes and less hemoptysis recurrence at 2-7d (odds ratio 3.03, p=0.05) and 30-180d (odds ratio 4.89, p=0.04). Of patients who lived at least 30 days post-BAE, those who were never re-hospitalized for hemoptysis (n=30) were older (p=0.01). They were also less likely to have multiple vessels embolized (odds ratio 0.32, p=0.04), immediate complications (0.17, p=0.003), bleeding at 7d (0.10, p=0.02), cystic fibrosis (0.24, p=0.02), asthma (0.31, p=0.05), or pneumonia (0.32, p=0.03). Survival analyses of these patients using hemoptysis recurrence as a primary endpoint reveal transfusion (p=0.01) and ICU (p=0.02) to correlate with better prognoses and cystic fibrosis (p=0.02) to be significantly associated with worse prognoses.

**Conclusions**: Malignancy and cystic fibrosis cause the majority of hemoptysis requiring BAE at our institution. The right and upper lungs are most frequently involved. Compared with 1998-2004, our outcomes in 2005-2011 were improved, which could reflect our growing experience. Our data suggest that patient risk factors for death within 30 days of BAE are immediate complications, bleeding at 7d, and a prior history of thoracic surgery. Risk factors for hemoptysis recurrence after BAE are multiple-vessel embolization procedures, immediate complications, bleeding at 7d, asthma, pneumonia, and cystic fibrosis. Conversely, the ICU and transfusions are linked to better outcomes.
The Development of Criteria for Assessing Surgical Intervention in Midshaft Clavicle Fractures

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Clavicle fractures are among the most common orthopedic injuries, constituting approximately 2.6-12% of all fractures and 35-44% of shoulder girdle injuries. Approximately 69-82% of clavicle fractures occur in the midshaft, or middle third of the clavicle. This area is highly prone to complications given its anatomic location and surrounding vascular supply. Subclavian injuries and large hematomas secondary to reinjury have been cited in the medical literature as complications of clavicular malunion. Many times neurovascular involvement can lead to permanent shoulder disability. Whether surgical intervention leads to better functional outcomes when compared to nonoperative treatment has long been debated. The importance of this controversy is revealed in the many retrospective studies looking at functional outcomes of patients.

Displacement during midshaft clavicle fractures are caused by muscle tension pulling apart the separate bone fragments. The sternocleidomastoid muscle pulls on the medial fragment superiorly and posteriorly, while the pectoralis major and deltoid pull the lateral fragment inferiorly and anteriorly. This causes a displacement between the fractured ends, with the lateral fragment lower. Shortening occurs when the pectoralis, trapezoid, and latissimus dorsi muscles pull the shoulder girdle medially.

We performed a literature review looking at 82 articles discussing the treatment for midshaft clavicle injuries and developed a common criteria set for recommending surgical intervention. Current indications for surgical treatment include open fractures, neurovascular involvement, skin compromise and wide separation of bone fragments with soft tissue interposition. Shortening exceeding 20 mm is an upcoming indication more commonly adopted by surgeons. Immediate indications for intervention include trauma to the chest wall, pneumothorax or hemothorax, and trauma that causes breaks to the scapular neck and body. Brachial plexus involvement in often rare, with the highest incidence being injury to the ulnar nerve because of its close location to the midshaft clavicle. Associated floating shoulder and scapular neck fractures are relative indications.

Avoidance of long-term sequaelae is the priority and indicators of surgical treatment have in the past been subjective based on various indicators surgeons foresee as resulting malunion, limitation of motion, and neurovascular involvement. Minimizing potential deformity and allowing the clavicle to heal via conservative treatment has not been shown in the literature to result in lower rates of nonunion and symptomatic malunion. We found that indications for nonsurgical treatment include minimally or nondisplaced midshaft clavicle breaks. These are further indicated by skin compromise or fractures that manifest with neurological and vascular injury involving multiple system trauma. Malunions, nonunions, and floating shoulders should be evaluated circumstantially and cautiously before recommending conservative treatment, immobilization, or slings.
Anti-angiogenic agents may enhance the effectiveness of breast cancer immune therapies

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The therapeutic benefit of induced tumoral immunity has yet to be realized in clinical settings. This is largely due to abnormal tumor vasculature. The tumor vessels are structurally (i.e., tortuous etc) and functionally (slow and heterogeneous perfusion) abnormal resulting in poor infiltration of T-lymphocytes and oxygen delivery. The T-cells that manage to go through the treacherous route of vasculature face a hypoxic tumor microenvironment that suppresses their functionality. This project aims to investigate the potential of anti-angiogenic agents to normalize tumor vasculature and to provide a therapeutic window for the efficacious action of tumor vaccines. We hypothesize that judicious use of an anti-angiogenic agent will normalize tumor vasculature reversing immunosuppressive microenvironment and facilitating T-cell infiltration and function. In order to accurately assess tumor immunity we used an orthotopically implanted syngeneic murine breast cancer model. Tumor tissue perfusion was analyzed by intravenous injection of Hoechst 33342 dye. Mosaic images of tumors were collected using a FV1000 Olympus Confocal Laser Scanning microscope. Non-specific nuclear staining (Sytox Green) was performed and used to exclude necrotic areas before analyzing tissue heterogeneity of perfusion. The findings from this project will make a major contribution to the development of optimally scheduled anti-angiogenic agents that will mitigate the immunosuppressive nature of the tumor microenvironment and improve the efficacy of immune therapies.
The effect of untreated antenatal depression versus antidepressants on neonatal health

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Antenatal depressive symptoms (major and minor depression) affect an estimated 18% of pregnant women. Antenatal depression poses risks for both the mother and the fetus, as untreated antenatal depression is associated with the mother’s decreased ability to perform daily activities, decreased ability to seek prenatal care, increased risk of smoking and alcohol use during pregnancy, and increased risk of self-harm and suicide. Untreated antenatal depression is associated with premature labor and stunted fetal growth as well as afflicted fetal temperament and childhood behavioral problems later in development. However, selective serotonin reuptake inhibitor (SSRI) use is associated with miscarriage, transient side effects due to abrupt withdrawal, and possible risk of pulmonary hypertension in infants.

Despite the wide variety of antidepressants available for treatment for antenatal depression, researchers and physicians have struggled with the risk of untreated depression versus the risk of antidepressants on both mother and fetus. In most studies that assess the effects of antidepressants on neonatal health, controls have been non-depressed pregnant women; the variables exclude the confounding factor of depression itself.

Based on previous studies, we expected the birth weights and APGAR scores of newborns of women who experienced antenatal depression to be less than those of newborns of psychiatrically healthy women; however, we were unsure of the comparative magnitude of the effect of antidepressant use and untreated depressive symptoms on birth weights and APGAR scores. To test these hypotheses, we used the Partners electronic medical database at the Brigham and Women’s Hospital and obtained all the medical records from obstetrical clinics that contained full Edinburgh Postpartum Depression Scale (EPDS) data (n=516). We then recorded the presence and dosage of SSRIs in prescription records. From electronic delivery room records, we were able to ascertain the APGAR scores and birth weights of the neonates of the women studied.

At this time, all of the EPDS and SSRI use data has been recorded; however, not all of the birth records are available. Once all data is available, we will perform a matched cohort analysis comparing birth weights and APGAR scores in symptomatic and asymptomatic women who did or did not take SSRIs during pregnancy. We were limited by the number of usable charts we could obtain.
The Effects of Direct to Consumer Advertising on Prescription Drug Sales: A Comparative International Analysis

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Background: The direct-to-consumer advertising (DTCA) of prescription drugs is defined as the promotion of prescription pharmaceuticals in the lay media (e.g. in radio, television, and magazines) and is distinct from the traditional means of promotion limited to medical professionals (e.g. detailing or advertisements in professional publications). It has been the subject of much controversy, and as of 2012, the United States and New Zealand are the only countries without explicit bans on DTCA. Previous research indicates that DTCA mainly increases the number of patients diagnosed for a certain condition and class-wide drug sales, with limited impact on individual sales for the advertised drug.

Objective: The majority of research on DTCA has focused solely on the US. We seek to more fully explore the effect of DTCA on drug sales by examining it in NZ, a country with different social, cultural, and legal structures, including a universal health care system and unique system of drug subsidization.

Methods: Our analysis will include a detailed examination of NZ government policy on medicines approval and subsidy to determine if DTCA’s effects on sales are modified by such wider structural factors. Australia – similar in culture, socioeconomic profile, government, and health care structure and financing to NZ – serves as a comparator, since DTCA is banned there.

The study focuses on the HMG-CoA Reductase Inhibitors (statins). We aim to collect data on drug sales for all statins marketed in Australia (Atorvastatin, Simvastatin, Pravastatin, Fluvastatin, and Rosuvastatin) and NZ (Atorvastatin, Simvastatin, Pravastatin, and Rosuvastatin) from 2005 to 2012. For each year, we will compare individual and statin-wide sales in (1)NZ, (2)Australia, and (3)between both countries, noting each individual drug’s subsidization status, price, and DTCA status in NZ.

Progress: At present, we are still awaiting data on NZ-wide drug sales from the NZ Ministry of Health, and anticipate it will be available by mid-September. Sales are quantified in both $NZD and by number of tablets sold, and are categorized by manufacturer and formulation. We await information about the DTCA status of the statins, and are seeking access to a comprehensive advertising database from AC Nielsen. Short-term plans are to complete the NZ-specific analysis, examining the role of DTCA and government policy on statin sales, while longer-term plans are to expand our analysis through the inclusion of data from Australia in order to contextualize DTCA’s impact on NZ drug sales, and strengthen the inferences drawn from the data.
Comparison of risk factors for cognitive decline across cancer survivors and women with no cancer history in the Nurses’ Health Study

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As cancer survivorship improves, it is important to understand effects of cancer and cancer treatments on health outcomes that are relevant in older age, such as cognitive function. However, epidemiologic data on the issue are mixed and more standardized methodology is needed to conduct rigorous epidemiologic research. This includes identification of suitable control groups when studying how cancer and/or cancer treatment may impact later cognitive health. This requires better knowledge of risk factor distributions for cognitive decline across groups of cancer patients and those with no history of cancer.

Here, we compared risk factor profiles for cognitive decline across breast, colorectal and uterine cancer survivors, as well as individuals with no history of cancer, in the Nurses’ Health Study (NHS). A secondary objective was to assess the potential influence of chemotherapy treatment, and elapsed time since cancer diagnosis on risk factors.

The NHS was established in 1976 when 121,700 female registered nurses completed a mailed questionnaire about health and lifestyle factors. For our analyses, we used risk factor data from the 2000 NHS questionnaire. Differences across groups were tested using chi-square tests for categorical variables and analysis of covariance for continuous variables.

We identified 6,159 breast cancer survivors diagnosed through the return of the 2000 NHS questionnaire, which included 5,220 (85%) invasive and 939 (15%) in-situ breast cancers. There were 876 colorectal cancer and 602 uterine cancer survivors. We identified 94,762 women who had no history of cancer.

After adjusting for age, distributions of risk factors for cognitive decline were generally similar across groups of cancer survivors and women with no cancer history. However, there was a higher proportion of uterine cancer survivors with BMI ≥ 30 kg/m² (40%) compared to the other groups (22-24%), and a higher percentage of uterine cancer survivors with type 2 diabetes (19%) compared to other groups in 2000 (9-11%). Similarly, a history of high blood pressure was more common among uterine cancer survivors (61%) than all other groups (48-52%).

We detected no qualitative differences in risk factor profiles for cognitive decline among past versus recently-diagnosed cancer survivors, or among breast cancer survivors treated with chemotherapy versus those not given chemotherapy (p>0.05).

These results suggest that for studies of cognition and breast and colorectal cancers, cancer-free populations may provide suitable and easily identified controls. However, the distinctive risk factor profile of uterine cancer survivors indicates that careful consideration must be taken in research on cognitive decline in this group.
Intrapartum Pain Management: 
Accurately Assessing Patients’ Wishes and Meeting Their Expectations

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Over four million obstetric deliveries occur in the United States each year. Options for pain management during childbirth are diverse, including parenteral narcotics, regional techniques, and non-pharmacologic methods. While utilization data depict highest rates of regional anesthesia, particularly epidurals, use may not denote preference or intent. Moreover, studies of patient satisfaction with childbirth highlight the importance of patient expectations, but it is unclear how strongly discordance between pain expectations and experiences can influence overall satisfaction. Furthermore, little data exist on how patients form their preferences for labor pain management, or whether departures from patients’ initial plans meaningfully impact satisfaction.

We aim to better understand the expectations of laboring women regarding intrapartum pain management, including preferences for different analgesic techniques, how those preferences are formed, and which factors most impact satisfaction. Two written surveys (utilizing NRS-11, Likert scales, multiple-choice and free-response questions) were administered to nulliparous women (n=30) presenting at term to BIDMC in either spontaneous labor or for labor induction; the first survey was administered prior to active labor or any pain management intervention and the second post-partum.

Preliminary results (n=14) indicate 79% of laboring patients intend to have an epidural, 14% plan a non-medicated birth, and 7% remain unsure at presentation. 100% ultimately received an epidural. On average, patients reported higher pain levels than they expected during active labor. Predicted and reported pain was not associated with patient age, gestational age, or expected baby size. Women in spontaneous labor predicted similar pain levels to those being induced, but reported higher experienced pain. Overall, women reporting labor was “more painful” than expected had lower overall satisfaction with their childbirth experience (3.4/5 vs 4.5/5).

50% of women cited friends/family as their primary source of information in making pain management decisions, while only 14.3% cited [their] obstetric provider. Although patients rarely selected the “internet” as their primary source, 71.4% said it impacted their decision. 57.1% of patients endorsed the concern that an epidural would slow their labor, 35.7% that it would provide insufficient pain relief, and 42.9% that they would experience a complication of catheter placement.

This work’s definitive goal is to inform potential improvements to patient care on labor and delivery in educational practices, counseling, and decision support for pain management in order to afford patients greater satisfaction in their childbirth experience.
Characterizing Novel Point Mutations in Metastatic Melanoma

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Most skin cancers are curable if detected early. Among the different types of skin cancer, melanoma is a cancer of melanocytes, the cells that produce melanin. Though other forms of skin cancer occur at higher rates, melanoma is highly metastatic and accounts for about 75% of deaths caused by skin cancers.

In recent work, Berger et al. (2012) used whole-genome sequencing to study the landscape of mutations in metastatic melanoma. DNA from 25 cancer samples were compared to their corresponding germline DNA. As expected, many mutations such as BRAF and NRAS, previously implicated in melanoma, were also commonly mutated in this sample set as well. Additionally, point mutations consistent with ultraviolet damage were seen as well. Though many mutations reported in this study and to date occur in coding regions, we have recently begun to study noncoding mutations detected by whole-genome sequencing of metastatic melanoma.

This summer, we have validated the presence of mutations in one of the genes identified. Furthermore, we found the presence of these mutations in several melanoma cell lines as well. Finally, reporter assays have shown that the studied mutations functionally affect the expression level of this gene. Overall, these data support the possibility of mutations in noncoding regions that may favor upregulation of prominent cancer pathways.
Evaluation of Discharge Care Coordination for Elderly Patients at an Academic Medical Center in Tokyo, Japan

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Coordination of appropriate discharge care is critical to reducing risk of readmission and facilitating optimal patient outcomes, particularly among elderly patient demographics. This is a particularly pressing issue in health care delivery in Japan, where declining birth rates combined with lengthening life expectancy are contributing to the highest rate of population aging in the industrialized world. Of the 128 million people in Japan, people over the age of 65 currently comprise 23% of the population and are expected to grow to 40% by 2050. Such aging trends coincide with high rates of inpatient care utilization, increasing complexity of health care for older patients, and shifting family structures that have resulted in a diminishing ability for families to provide appropriate discharge care for elderly family members. With these social factors and growing gaps in care provision for the elderly, there is an urgent need to ensure that timely and appropriate discharge care is being provided to elderly patients.

The overall objectives of this project were to investigate the care transition process at the Tokyo Medical and Dental University (TMDU) University Hospital of Medicine, a large academic medical center in Tokyo. Research was conducted at the TMDU Center for Medical Welfare and Support, a department established in 2007 to provide dedicated social welfare and discharge coordination to patients of the TMDU University Hospital. The Center for Medical Welfare and Support oversees discharge care for four major patient demographics: Emergency Department discharge, neurosurgery, pulmonology, and neurology. The specific aims of this project were to characterize the elderly demographic of patients receiving discharge services from the center while understanding the discharge care coordination paradigm for elderly patients. Subsequently, this research sought to identify the operational, institutional, and cultural factors that define strengths and challenges in the current discharge coordination process.

A combination of historical data analysis, patient interviews, and provider discussions were conducted. The Center for Medical Welfare and Support provides discharge coordination for a high volume of medically-complex cases, servicing an approximately 700 cases in 2011. Stakeholder interviews revealed a high degree of patient satisfaction but also indicated a need for greater institutional engagement in creating a standardized approach to discharge coordination and communication of discharge planning. This project provides a foundation for achieving a broader perspective of the opportunities, obstacles, and future trends facing medical welfare and support services at publically-funded, academic medical institutions in Japan.
Adverse cutaneous drug eruptions encompass several cutaneous disorders including fixed drug eruptions, erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). The mortality of severe ACDEs remains high at a rate of 5-15% for Stevens-Johnson syndrome and TEN, which may represent a more serious form of SJS, has a reported mortality of 25-70%. Thus, there is need for investigation into new treatment modalities for ACDEs, and immunological mediators involved in the pathogenesis of ACDEs, such as effector CD8(+) T cells or Tregs, that may serve as potential targets for such new therapies.

While certain drugs such as sulfonamides, anticonvulsants, and NSAIDs are known triggers of ACDEs, HIV-infection is a well-known risk factor for ACDEs. This finding has been attributed to the widespread use of sulfam-containing, anti-retroviral, antituberculous agents in this population as well as infection with the HIV virus itself. The HIV virus is tropic for CD4(+) cells and decreasing CD4 counts have been previously correlated with increased incidence of ACDEs.

A portion of the CD4+ T cells present in skin are a subset called regulatory T cells (Tregs), which function to suppress CD4(+) cells and CD8(+) effector T cells and have a role in establishing self-tolerance and immunological anergy. We hypothesize that in HIV-infected individuals a decreased number of CD4(+) cells leads to lower expression of Tregs in the skin and causes unregulated CD8(+) activity in the skin that may be responsible for the higher incidence of ACDEs seen in HIV-infected versus non-infected hosts.

Using immunohistochemistry to identify CD8(+), CD4(+), CD25(+) T cells within skin biopsies of TEN from HIV-infected and non HIV-infected controls, we have found a significant decrease in CD4(+) cells, an increase in the ratio of CD8(+) to CD4(+) cells, and a decrease in CD25(+) cells among skin afflicted with TEN from HIV-positive hosts. Such data suggest that the increased risk to TEN in HIV infected skin may be attributed to altered immunological function secondary to the HIV virus and also identifies Tregs as an important mediator and potential target for future TEN therapy.
The mTorc2-Akt1 Signaling Axis Increases Tumor Fitness through Regulation of Slowly-cycling Cancer Cells

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Rapidly proliferating cancer cell populations in both \textit{in vivo} and \textit{in vitro} settings have been shown to contain out-of-cycle cells that play a functional role in maintaining tumor viability. Unlike the classic hierarchical stem-cell model, these slowly cycling cells, which we have previously characterized to have a distinct immunohistochemical profile (MKI67\textsuperscript{low}, MCM2\textsuperscript{low}, CDC6\textsuperscript{low}, GMNN\textsuperscript{low}), are continuously generated from a bulk tumor population and can revert back into an actively cycling state within a few days \textit{in vitro}. We have previously demonstrated that the Akt1 signaling pathway can regulate this proliferative heterogeneity, but the upstream regulator remains unknown.

There are two main upstream regulators of Akt1: the canonical PDK1 pathway which phosphorylates Akt1 at T308 or relatively lesser well-characterized mTorc2 complex which phosphorylates Akt1 at S473. Our main objective is to characterize which of these upstream pathways plays the predominant role in driving the slowly-cycling subpopulation and to demonstrate the important of this pathway for tumor growth and survival.

In order to elucidate the upstream mechanism, we created 17 mutant variants of Akt1 that perturb either a specific amino acid residue or region that is known to influence the up- or downstream signaling and introduce the mutants into an Akt1/2 knockdown colon cancer cell line. To complement our genetic approach, we also use small-molecule inhibitors and small-hairpin RNAs targeting the Rictor protein in the mTorc2 complex to induce the phenotype in wildtype cell lines. We identify slowly-cycling cells based on immunohistochemistry profiling. In order to functionally characterize our phenotype, we perform live-cell imaging to study cellular kinetics and tested viability of enriched or depleted population of slowly-cycling cells under chemo-radiation therapy and when transplanted into nude mice.

Alanine mutagenesis of T450 and S473 in Akt1 disrupts the formation of slowly-cycling cells. Combined torc1/2 inhibition but not torc1 inhibition alone eliminated the phenotype, as do small-hairpin RNAs that selectively disrupt the mTorc2 complex. Elimination of the slowly-cycling phenotype using inducible shRNA against Rictor increases overall sensitivity to chemo-radiation therapy and also results in poorer tumor xenograft growth \textit{in vivo}. Enrichment of the slowly-cycling phenotype using chemical inhibition of Akt1 resulted in larger tumors \textit{in vivo} compared to control.

These findings suggest that the mTorc2-Akt1 signaling axis is necessary to generate and maintain a slowly-cycling subpopulation in cancer cells, and that these cells are important for the growth and hardiness of the overall survival of the tumor.
Analysis of Water Distribution System and Hygiene Practices in Rural Villages of Mchinji, Malawi

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While there is a report by WHO that up to 80% of the water in rural Malawi was from improved sources like boreholes and protected wells, there is no concrete data on the availability and quality of these water sources in villages. In addition, there is no qualitative data on how the villagers perceive water sanitation when obtaining and using water from different water sources. This study aims to find out the locations of main water sources in eight rural villages and villagers’ self-identified problems and hygiene practices around them.

Eight rural villages in Mchinji district of Malawi were randomly selected, and the main water sources were located in summer of 2011 by asking villagers where their main source of water is located within each village. In the summer of 2012, the previously identified and newly established water sources were mapped using Garmin Oregon 550 GPS. Qualitative interviews were then conducted on a convenience sample of random villagers in order to identify which water source(s) they use and how they perceive the water source(s) in terms of convenience and quality. The interviewed villagers’ houses were also mapped using the GPS in order to identify any apparent differences or similarities amongst villagers in relation to where they are located.

In most villages, protected or treated water sources like boreholes and public taps are located at centrally, used by all villagers as the main drinking water, and are often maintained well. But villagers have limited access to these due to distance and wait time. Wells – covered or uncovered – are used by villagers around them as their secondary water sources and aren’t maintained as well. Existing organizations such as a committee looking over a certain borehole or a protected well for its maintenance were at the level of small compound within a village and not at the level of the entire village. In addition, villagers still rely heavily upon untreated wells or stream water for daily usage despite the protected water sources, maintenance of protected water sources can become a burden, and there is no governmental effort to identify the imbalance in existing water sources amongst villages in order to distribute water sources evenly throughout the villages.

In order to solve the problem of apparent shortage in quality water, easy water treatment like bleaching is the cheapest way for the villagers. Village-wide organization is necessary for continuous availability of quality water.
Hyperlactatemia is typically present in patients with severe sepsis or systemic inflammatory response syndrome (SIRS) and secondary to anaerobic metabolism due to hypoperfusion. The prognostic value of elevated blood lactate levels is well established. Trends in serum lactate levels represent patient response to treatments and progress of disease process, necessitating repeated lactate tests. An increase in levels signifies ineffectual therapy, while decrease in levels in the setting of relative hypotension can reassure clinicians and prevent overuse of potentially harmful treatments (e.g. vasopressor therapy or excessive fluid volume). However, the significant turnaround time for lactate laboratory tests (1-2 hours) impedes the time-sensitive determination of such trends. Furthermore, frequent blood draws for such tests may result in iatrogenic anemia and false positive results.

Our objective is to model patient response to treatments during critical illness for improved prognostication. We hypothesized that serum lactate levels correlate with other documented variables and aimed to create a model for predicting change in lactate values based on physiological variables, medications, and other laboratory data.

We performed a retrospective cohort study on patients from MIMIC-II, a publicly available de-identified clinical database from the Beth Israel Deaconess Medical Center. The Martin sepsis criterion was used to identify the sepsis and SIRS cohort which collectively had 20064 serum lactate tests. For each test, the previous lactate test value and several potential variables were extracted from the database, including: blood pressure, heart rate, respiratory rate, spO2, temperature, vasopressors, analgesia, sedation, fluid intake, blood and plasma transfusions, and urine output. Aggregate statistics, flags, and changes in these variables were calculated as potential variables for model generation.

Lactate tests without previous physiological variables were excluded, leaving 15950 data points. This group was further randomly divided into training, checking, and validating sets. Variable selection was performed on the training and checking sets using either forward selection or a genetic algorithm with fuzzy logic selection criteria. The resulting model was tested on the validating set and achieved an area under the curve of 0.65.

This preliminary result suggests that changes in serum lactate values may not be predictable using correlated variables. However, patients that present with a lactate value >4mmol/L generally have a very different course of disease than patients with a lactate value <4mmol/L. We will next partition the cohort into two based on presenting lactate value (> or <4mmol/L), and include more variables, such as clotting factors and hematocrit, for consideration.
Is Rwanda a Model for Effective Aid Policy Implementation

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In 1994, an estimated 800,000 people were massacred in the Rwandan Genocide. The conflict bore its toll on the economy, which showed a 64% increase in inflation and a 50% decrease in growth. The country has made strides in recent years, where Rwanda’s GDP growth rate has increased an average rate of 8.5% between 2008-2012. Given these recent gains, I investigated whether Rwanda’s effective usage of aid is responsible for Rwanda’s recent successes.

In 2006, Rwanda underwent a series of reformations of its national aid policy that transformed the way development assistance was handled. This aid policy was paired with a new national economic development and poverty reduction strategy executed in 2008. These new policies shifted aid modalities towards budget support, and mandated that assistance be aligned with government priorities. In an effort to improve public financial management systems, joint oversight and steering committees were formed to monitor aid disbursement as reflected in a newly created development assistance database. As a result of these changes, aid reflected in the national budget rose to 71% in 2010 from 51% in 2007. Moreover, a comprehensive division of labor agreement was enacted with donors that distributed sector involvement by maximizing comparative advantage. In terms of technical assistance, efforts have been focused on strengthening local capacity as opposed to traditional gap filling roles. This is evidenced by a recent $20 million joint capacity development program launched by the World Bank and the government of Rwanda (GoR) designed to strengthen the country’s civil service. The government has also partnered with donors to ensure that its policies and services fully benefit its citizens. The GoR has implemented feedback mechanisms through its use of citizen report cards and community score card surveys as a way to assess Rwandan citizens’ perception of the quality, adequacy and efficiency of public services.

All in all, the successful implementation of these policies did not go unnoticed, where Rwanda was only one of two developing countries to earn an “A” rating from the OECD for its national development strategy. Rwanda’s success policy carries valuable lessons for donors and governments of other developing and post-conflict nations in implementing effective aid policy.
Implementation and Assessment of Community-based, Decentralized Non-communicable Disease Clinics

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Non-communicable diseases (NCDs) represent a growing burden of disease in Rwanda, accounting for 29 percent of mortality. Rwanda’s rural population faces significant challenges in access to NCD treatment.

Partners in Health (PIH), along with the Rwandan Ministry of Health, established NCD clinics at three rural district hospitals to address these gaps in care. To further expand access, systematic decentralization of NCD treatment to community-based health centers (HCs) was initiated in June 2012 at Kabarondo HC (catchment 35,500). The goal was nurse-management of uncomplicated cases of diabetes, hypertension, heart failure and chronic respiratory disease (CRD) and integration of NCD care with existing chronic infectious diseases (ID) services. This process included development of operational assessments, protocols for HC-based NCD treatment, training of HC nurses, and expansion of the electronic medical record (EMR) to include NCDs.

Three Kabarondo ID-trained nurses underwent NCD training at Rwinkwavu, to serve as integrated chronic care nurses supported by ongoing site-based mentoring. A data officer was trained to enter data from paper NCD charts into EMR, and data quality was reviewed weekly. A NCD clinic room was outfitted adjacent to the ID clinic. Weekly monitoring of clinical services, staffing, infrastructure and availability of medications, laboratory consumables, and equipment stared two weeks before clinic launch. Data were used in real-time to identify and address gaps with feedback given to relevant teams.

Current eligible patients from the Kabarondo area were transferred from Rwinkwavu Hospital to Kabarondo HC. New patients presenting at Kabarondo HC underwent diagnostic evaluation at Rwinkwavu Hospital to determine appropriate site of care. The number of patient visits per clinic ranged between 3 to 18 patients, and totaled of 35 over the first month. A majority of visits were for hypertension (18) and CRD (11). All patients were adults and 68 percent female. Main challenges included high patient volume, medications stockouts, and inconsistent nurse availability. Solutions have included: ongoing supply-chain support, clinic appointment scheduling to maintain patient load at 10-15 per clinic, and hiring of new personnel to address the departure of one nurse due to personal circumstances.

The initial launch of Kabarondo’s NCD clinic was successful overall; ongoing work continues to address challenges and evaluate progress, with thorough reviews planned at 3 and 6 months. It is anticipated that the clinic will continue to grow in size, training of skilled nurses will expand to include other chronic diseases spheres such as mental health and palliative care, and the clinic will inform decentralization of care to other health center facilities.
Role of numeracy and genetic literacy in the desire to receive genetic risk information

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Purpose: Whole genome sequencing (WGS) will soon be integrated into clinical medicine, but the question of what genetic risk information should be returned to patients remains unresolved. Answering this will be based in part on patients’ comprehension. We investigated the association of numeracy and genetic literacy with interest in genetic risk information.

Methods: We assessed responses from a population-based cohort surveyed on interest in WGS. Numeracy was assessed by a validated scale of three probability questions. Genetic literacy was assessed using eight genetic knowledge questions. Logistic regression determined associations of numeracy and literacy with interest in risk information.

Results: Numeracy and genetic literacy predicted overall interest in WGS. Numeracy predicted interest in curable disease (p=0.027), treatable but incurable disease (p=0.004), preventable disease (p=0.004), addiction (p<0.001), infertility (p=0.050), and which medications will work (p=0.013). Literacy predicted interest in mental illness (p=0.016). Neither numeracy nor genetic literacy predicted interest in incurable disease, risk of passing disease to children, sexual preference, and physical traits such as balding.

Conclusion: Numeracy and genetic literacy predicted interest in WGS, but when risk information was subcategorized the associations held for some traits but not others. Understanding how patient characteristics predict interest in genetic risk information can help providers tailor discussions with diverse patient populations.
An Intervention to Improve Stethoscope Disinfection in a Children’s Hospital

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Background: Stethoscopes are contaminated with pathogenic bacteria and pose a risk for transmission of infections. Fewer than 25% of pediatric healthcare providers disinfect their stethoscope after every use, and lack of access to disinfection materials and lack of visual reminders are associated with lower disinfection rates.

Objective: To implement an intervention to improve stethoscope disinfection at a pediatric hospital and assess the impact on disinfection rates.

Methods: We conducted a prospective intervention study of physicians and nurses in inpatient units and the emergency department at Boston Children’s Hospital in July-Aug 2012. The study had three phases: 1) direct observation of baseline stethoscope disinfection practices; 2) installation of baskets filled with alcohol swabs and a sticker reminding providers to regularly disinfect stethoscopes outside of patient rooms, followed by a 3-week washout period; 3) direct observation of post-intervention stethoscope disinfection practices. Waiver of informed consent was granted so that participants were unaware of the behavior being observed. The primary outcome was the proportion of stethoscope disinfection opportunities in which disinfection was performed. Multivariate logistic regression models were created to identify independent predictors of stethoscope disinfection, adjusting for potential confounders such as type of unit, time/day of week, and provider role.

Results: There were 226 observations in the pre-intervention period and 261 in the post-intervention period (83% were of physicians). Between periods, 206 baskets were installed hospital-wide and filled with alcohol swabs. Stethoscope disinfection compliance increased significantly from a baseline of 34% to 59% post-intervention (p<0.001). In adjusted analyses, the post-intervention period was associated with improved disinfection among both physicians (OR 2.5, 95% CI 1.6-3.9) and nurses (OR 17.3, 95% CI 5.4-55.5). Additional independent predictors of disinfection included subspecialty unit (vs. general pediatrics, OR 3.2, 95% CI 1.8-5.7) and contact precautions (OR 2.4, 95% CI 1.3-4.5).

Conclusions: Providing stethoscope disinfection supplies and visible reminders outside of patient rooms significantly increased stethoscope disinfection rates among physicians and nurses at a children’s hospital. This simple intervention could be replicated at other healthcare facilities. Future research should assess the impact on patient infections.
Thermochromic Uterine Sound

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Uterine sounding is the process by which a metal or plastic probe is inserted through the external cervical os into the tip of the uterus in order to gauge uterine depth. The thermochromic uterine sound is an improvement on existing uterine sounding devices used extensively in the office and operating room for the measurement of uterine length, typically before procedural intervention. Sounding the uterus is crucial for an accurate assessment of uterine length to reduce the risk of uterine perforation during subsequent instrument insertions. In the primary care setting, sounding is most often routinely performed prior to the insertion of intrauterine devices (IUDs).

Current uterine sounds are graduated, but the examiner must use either a finger at the external cervical os to mark the level of maximal insertion, or else use blood or discharge on the sound to estimate the level of maximal insertion. The thermochromic uterine sound is a sounding device coated with a layer of thermochromic ink designed to change color at temperatures close to body temperature. As the instrument is inserted through the external cervical os, portions of the sound distal to the os will be subject to aforementioned critical temperatures, and upon removal of the sound, the examiner has an easily accessible visual denotation of the level of maximal insertion.

Thermochromic technologies have never been applied to uterine sounding. The advantages of the thermochromic uterine sound are threefold: (1) The thermochromic sound offers convenience to the examiner, (2) comfort to the patient, and (3) a more accurate measurement of uterine length. Measures of success of this new medical device include subjective ratings of user satisfaction, including both ease of use and time saved, patient comfort, and incidence of complications, including uterine perforation. The innovation is currently pending U.S. patent.
Rare Variants in Genes Implicated in GnRH Deficiency in Patients with Constitutional Delay of Growth and Puberty

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Background: Constitutional Delay of Growth and Puberty (CDGP) is characterized by a lack of sexual maturation greater than 2 standard deviations above the mean for a population (approximately 13 years of age for girls and 14 for boys) not associated with any other medical condition. Though the timing of puberty has been shown to be a heritable trait, the genetics of delayed puberty are not well understood. However, several genes have been implicated in Idiopathic Hypogonadotropic Hypogonadism (IHH), a congenital form of GnRH deficiency characterized by a lack of or incomplete pubertal development by age 18. We hypothesized that mutations in genes implicated in the rare condition IHH increases the risk of developing the more common condition CDGP.

Methods: To test the hypothesis, we analyzed the coding sequence of genes implicated in GnRH deficiency (GNRHR, GNRH1, KISS1R, KISS1, FGFR1, FGF8, PROK2, PROK2, TAC3, TACR3, CHD7, NELF, HS6ST1, and KAL1) in 31 CDGP men and women with no prior family history of IHH and 27 CDGP men and women with a family history of IHH for rare sequence variants. We characterized the pathogenicity of the identified rare variants by in silico analysis and performance in previously reported in vitro functional assays. For CDGP subjects with a family history of IHH, we compared the incidence of pathogenic rare variants between CDGP subjects and unaffected family members. For CDGP subjects with no family history of IHH, we compared the incidence of pathogenic rare variants between CDGP subjects and a cohort of 192 controls with normal pubertal development. We used Fisher’s exact test to identify statistically significant differences (P ≤ 0.01) in pathogenic rare variant frequencies.

Results: Thirteen out of 27 CDGP subjects with a family history of IHH were found to have heterozygous pathogenic rare variants compared to 7 out of 40 unaffected family members (P = 0.01). Relative risk of developing CDGP in subjects with pathogenic rare variant(s) compared to subjects without pathogenic rare variant(s) was 2.8 (95% CI, 1.3-6.0). Five out of 31 CDGP subjects with no family history of IHH were found to have heterozygous pathogenic rare variants compared to 6 out of 192 unaffected controls (P = 0.01). Relative risk of developing CDGP in subjects with pathogenic rare variant(s) compared to patients without pathogenic rare variant(s) was 5.2 (95% CI, 1.7 to 15.9).

Conclusions: Pathogenic rare variants in genes implicated in IHH are found at a higher frequency in individuals with constitutional delay of growth and puberty than in unaffected controls, suggesting that these pathogenic rare variants convey an increased risk for developing the CDGP phenotype. Our observations provide evidence for the role of rare variants in common multifactorial disease.