74th Annual
Soma Weiss
Medical and Dental
Student Research Day

January 16, 2014

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

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

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

Harvard Medical School wishes to thank the Weiss family for their generous support of the Annual Soma Weiss Student Research Day.
Soma Weiss
1899 - 1942
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Soma Weiss Student Research Day
January 16, 2014

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 209, Tosteson Medical Education Center

Welcome
Jules Dienstag, MD, Carl W. Walter Professor of Medicine; Dean for Medical Education, Harvard Medical School

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

Student Speakers
Emilie Mitten (Holmes)
Physiologic investigation of the renin-angiotensin-aldosterone system in HIV patients
Lisa Rosenfeld (Peabody)
Assessing the use of interactive voice response technology in a smoking cessation intervention
Anna Jo Smith (Cannon)
The potential impact of health insurance exchanges on children’s health insurance access and coverage
Caleb Yeung (London)
Cleavage of the anaplastic lymphoma kinase in neuroblastoma

Awarding of Poster Prizes
Elizabeth D. Hay Prize for Basic Science Research
Judah Folkman Prize for Clinical / Translational Science Research
Charles Janeway Prize for International Research or Service
Robert Ebert Prize for Health Care Delivery Research or Service
Leon Eisenberg Prize for Medicine in Society Research
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Efficacy of Transfection of Inner and Outer Hair Cells Using Adeno-Associated Virus

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Over 36 million individuals in the U.S. and over 250 million worldwide suffer from hearing loss. Damage to a crucial sensory organ like the inner ear can result in serious cognitive and behavioral impairment in young children and gradual decline in hearing can be incredibly disruptive and inhibitive in older populations.

Aside from hearing devices, no direct therapy exists to treat hearing loss. Hair cell regeneration and exogenous gene therapy are potential treatments. Loss of transmembrane cochlear expressed gene 1 (TMC1), which encodes a transmembrane protein of unknown function, is necessary for the normal functional maturation and survival of inner and outer ear cells in the mouse cochlea. The presence of Tmc1 in both inner and outer hair cells in early postnatal development suggests the importance of this protein in auditory function. Viral delivery of therapeutic genes could potentially target these sites, particularly in the inner ear. Different viruses have been studied previously, and adeno-associated virus has been found to be the least immunoreactive vector.

We hypothesized that certain serotypes of adeno-associated virus are more effective at targeting and delivering genes of interest to inner and outer hair cells. 1) Expression of GFP driven by a CMV promoter was used as a reporter for hair cell transfection by AAV serotypes 1, 2, 6, 8, and 9. Cochlear tissue from post-natal day 0 mice (P0) was transfected with these serotypes in a range of effective concentrations from approximately 1E10 to 1E11. P0 cochleas were transfected for 24 hours and subsequently cultured for 7 days. Cochleas were fixed then imaged and cell transfection rates were subsequently quantified.

Results indicate that the AAV1 serotype demonstrates the greatest level of transfection rate, with an average of approximately 53.87% at an effective concentration of 6.67E10 vp/μL throughout the entire cochlea. The transfection rates for the other serotypes were as follows: AAV2 was 10.61%, AAV6 18.78%, AAV8 25.28%, AAV9 12.7%. The effect of differ viral titers was also evaluated for the most effective serotype AAV1. The transfection rate was found to be highest toward the base of the cochlea and decreased approaching the apex.

AAV1 viral vectors serve as a potential vehicle for delivering in vivo gene therapy in hearing loss patients. Future experiments will evaluate the role of specific promoters in upregulating gene expression in vivo (e.g. Beta-actin, CMV, MYO6 or MYO9) and rescuing hearing function in Tmc1 knock out mouse models.
Identifying Disease Genes in a Mutation-Negative Cohort of Congenital Fibrosis of the Extraocular Muscles

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Congenital fibrosis of the extraocular muscles (CFEOM) refers to a group of rare strabismus syndromes, where patients present with nonprogressive, restrictive ophthalmoplegia (inability to move the eyes in certain directions), with or without ptosis (drooping eyelids). CFEOM is characterized as an orphan disease because it affects less than 1% of the population, with a minimum prevalence of one in 230,000. Patients with this disorder present with a range of visual impairments, which may include loss of binocular vision, high astigmatism, and poor or blurry vision due to amblyopia. Other non-visual defects may include developmental delay and central and peripheral neuropathies. Mutations known to cause CFEOM have been localized to genes involved in axon guidance, particularly those that alter cytoskeletal arrangement and microtubule dynamics. While the genetic basis of the disorder has been identified in many affected individuals, there remains a cohort who does not carry mutations in these known genes. Through whole exome sequencing (WES) analysis, our goal was to find candidate genes, which may be involved in conferring the CFEOM phenotype in this cohort.

Individuals in this mutation-negative cohort were organized based on similar characteristics: those that share gastrointestinal and muscular abnormalities and/or those who have a comparable isolated CFEOM presentation. Through whole exome sequencing analysis, we have identified candidate genes, in which at least two families hold potentially pathogenic mutations. These genes include MICAL1, LIMD1, and ANKK1, which are known to be involved in cytoskeletal organization and/or signal transduction in the central nervous system. In future studies, we would like to conduct Sanger sequencing to confirm mutations in these genes and validate appropriate segregation of the potential disease-causing allele within families. Once this has been done, we will screen a larger cohort of CFEOM probands for mutations within these genes, which would provide further support for a causal link between these genes and CFEOM.
Investigating Incidence of Fabry Disease in Patients with Cryptogenic/Ischemic Stroke

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Fabry disease is a genetic disorder that is treatable with currently available FDA approved therapies. Early identification and therapy can dramatically slow its progression towards end-organ failure. However, it has been shown that patients will, on average, go five years without being properly diagnosed after their first symptom. It has been hypothesized that Fabry is an underdiagnosed cause of vascular disease and its associated end organ disease. The goal of this project is to assess the incidence of Fabry in patients less than 55 years of age who have suffered from stroke that has no other diagnosed explanation. We expect this data to add to our epidemiologic knowledge of Fabry disease by showing it is an underdiagnosed cause of idiopathic stroke. We hope that highlighting the prevalence of Fabry in the young stroke population will heighten physician awareness, lead to identification of affected probands, and allow important genetic risk assessment in their families.

DNA was collected from 160 male and female patients who have suffered a cryptogenic stroke. Their DNA was examined using the Biofire Diagnostics LightScanner™ high resolution DNA melting technology. Differential melting and migration are used to screen for DNA mutation. Full coding region Sanger sequencing was done on positive cases, where a single mutation in the gene had been found, for mutation identification. Lastly, I analyzed the data and determined the prevalence in this cohort.

Out of 160 patients 93 males and 64 females (157 total) were analyzed; 3 were not included in the final analysis. From the 157 tested, 51 (32%) patients came up positive for non-pathogenic polymorphisms. There are 2 (1.3%) mutations that were found and may be indicative of Fabry. One mutation found was c.8 T>C L3P and the other C.1202 C>A S401X. Lastly, there were 4 (2.5%) mutations found in intron 4, g.9278 del AG, that have been suspected in also causing the disease. All together the number of mutations found was 6 out of 157 and this leads to an incidence of 3.8%. This is a much higher rate than found in previous whole populace studies.

These data show Fabry disease should be considered in any patients that are showing any signs of early stroke, autonomic dysfunction small fiber neuropathy with chronic pain, proteinuric renal failure and hypertrophic cardiomyopathy with risk of heart failure and arrhythmia.
Association of Fat Quality with Subclinical Atherosclerosis

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Ectopic fat quality is associated with cardiovascular disease (CVD) risk factors above and beyond fat volume. Volumetric measures of ectopic fat have been associated with CVD risk factors and subclinical atherosclerosis. The aim of this study was to investigate the association between fat quality and subclinical atherosclerosis.

Participants were drawn from the Multi-Detector Computed Tomography (MDCT) sub-study of the Framingham Heart Study (n=3,079, mean age 50.1 years, 49.2% women). Fat quality was measured via CT attenuation (Hounsfield Units [HU]). Visceral fat (VAT), subcutaneous fat (SAT), and pericardial fat HU and volumes were quantified using standard protocols; coronary and abdominal aortic calcium (CAC and AAC, respectively) were measured radiographically. Multivariable-adjusted logistic regression models were used to evaluate the association between adipose tissue HU and the presence of CAC and AAC. Overall, 17.1% of the participants had elevated CAC (Agatston score>100), and 23.3% had elevated AAC (Agatston score>age/sex-specific cutoffs). Per 5-unit decrement in VAT HU, the odds of elevated CAC were 24% lower (OR 0.76, 95% CI 0.65-0.89, p=0.0005), even after adjustment for BMI or VAT volume. Results were similar for SAT HU. With decreasing VAT HU, we also observed 21% lower (OR 0.79, 95% CI 0.67-0.92, p=0.004) odds of elevated AAC after multivariable adjustment. We found no association between SAT HU and AAC. There was no association between pericardial fat HU and either CAC or AAC.

Lower VAT and SAT HU, indirect estimates of fat quality, are associated with a lower risk of subclinical atherosclerosis.
Identification and Validation of Novel Biomarkers for Prostate Cancer

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Prostate cancer (CaP) is one of the most commonly diagnosed malignancies in men in the United States. With 241,740 estimated new cases and 28,170 estimated deaths in 2012, it remains the second leading cause of cancer death in American males. Accurate screening for CaP is of critical importance as patients typically do not present with symptoms until the disease has become locally advanced or metastatic. Currently, prostate-specific antigen (PSA) testing is the clinically accepted standard for prostate cancer screening, but its effectiveness is far from ideal. Specifically, PSA lacks specificity and fails to differentiate between indolent and aggressive forms of disease most likely to cause mortality.

Based on these striking facts, we sought to investigate the existence of novel biomarkers by utilizing several genetically engineered mouse models (GEMMs) of human CaP. By profiling and studying the “secretome” of androgen deprivation therapy (ADT)-sensitive and ADT-resistant murine prostate cancers, we believe there exists the potential to identify a correlated signature of these subsets.

We thus analyzed microarray expression profiles and mass spectrometric proteomic studies of prostate tumors collected from cohorts of several well-established models, including Pten-null, Pten/Lrf-null, and Pten/PML-null mice. We identified several secreted proteins upregulated in prostate tumors as compared to age-matched controls, among them being Spink3, Osteopontin, Osteocalcin and Clusterin. The presence of these proteins, whose human homologues are well-known genes exhibiting overexpression human CaP, confirms the robustness of our approach and identifies our GEMMs as promising tools to study the role of these oncoproteins in tumor growth, invasion and therapeutic response.

We chose to focus our attention on Spink3, as overexpression of the human homologue Spink1 is frequently described in CaP, especially in TMPRSS2-ERG negative tumors, although its oncogenic function remains a matter of debate. To characterize the role of Spink1/Spink3 during CaP development, we utilized a panel of genetically stratified GEMMs of human CaP and analyzed the expression levels of Spink3 transcript and protein in prostate tumor samples via RT-qPCR and WB and IHC, respectively. Ultimately, we employed an ELISA approach to assess the possible presence and variation of Spink3 levels in the serum of our GEMMs.

Since Spink3 overexpression appears to characterize ADT-resistant murine prostate tumors more than ADT-sensitive tumors, we are now evaluating the possible function of human Spink1 in androgen depletion sensitivity using the human CaP cell lines VCaP and LnCaP as well as the immortalized human prostate epithelial cell lines RWPE1 and PWRE1.
Development of a Patient Decision Aid for Aortic Valve Replacement Surgery

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The mechanical valve and tissue valve have similar benefits but different potential drawbacks and harms. As a result, the best option depends on how patients feel about these considerations. Currently, clinicians at Massachusetts General Hospital explain the type of valve decision in the office consultation, with no formal structure or additional shared decision making materials provided to patients. A patient decision aid (DA) was developed to provide consistent, clear information and to support patient engagement in decision making.

A needs assessment examined key challenges for clinicians and patients in making treatment decisions between the tissue and the mechanical valve. Key informant interviews were conducted with four cardiac surgeons, three cardiologists, and three patients. These discussions identified key challenges in accessing risk estimate information, communicating complex information under time constraints, and conflicting recommendations from different specialists. Interviewees agreed that a DA would be helpful in addressing these challenges.

Development of the prototype DA followed standardized methodology outlined by the International Patient Decision Aid Standards Collaboration’s twelve criteria for the systematic development of decision aids. These criteria include such items as appropriate methods of providing information to patients about options, presenting probabilities, clarifying and expressing values, and addressing health literacy.

Preliminary feedback from clinicians and patients is positive. We are currently designing a randomized control trial to study the tool’s effectiveness in increasing patient knowledge, reducing decisional conflict, and increasing alignment between patients’ choices and their goals and preferences.
Ethnic and Gender Diversity of Hand Surgery Trainees Compared to Other Specialty Trainees

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In 2010, White Americans made up a record low of 72.4% of the US population. In the US, increasing diversity in ethnicity, race, and gender in the healthcare arena showed improved patient outcome. However, orthopedic surgery currently lags behind other medical fields in ethnic and gender diversity. We predict that orthopedic hand surgery trainees have remained relatively homogenous and less diverse than other specialties during 1995-2011.

The ethnic and gender composition of ACGME certified trainees from 1995-2011 were analyzed using data published in Journal of the American Medical Associated (JAMA). Changes in ethnic and gender composition were analyzed using the Wald chi-square test and the Z-test. \( p<0.05 \) was considered statistically significant.

Out of the Asian, Black, and Hispanic hand and orthopedic trainee population, only the Hispanic hand population did not show a significant increase from 1995-2011. Hand: \((0.40\%, 0.20\%, 0.079\% \text{ increase per year}; p=0.019, p=0.011, p=0.458)\). Orthopedics: \((0.95\%, 0.11\%, 0.13\% \text{ increase per year}; p<0.001, p=0.051, p=0.010)\).

Currently, Asians represent largest proportion of non-White trainees in both hand and orthopedics. However, % Asian orthopedic trainees is increasing significantly faster than their counterparts in hand surgery \((0.95\% \text{ vs. } 0.50\% \text{ increase per year}; p<0.001)\).

Percentage of non-White hand trainees is not significantly different from that of general surgery, orthopedic surgery, neurological surgery, and orthopedic sports medicine. \((p=0.93; p=0.99; p=0.94; p=0.11)\).

Growth of female hand surgery trainees \((+0.65\%/\text{year})\) is not significantly faster than that of female orthopedic surgery trainees \((+0.34\%/\text{year})\) \((p=0.098)\). Significantly more female hand surgery trainees than female orthopedic surgery trainees every year except 1999 \((p<0.001)\).

% female hand surgery trainees \((19.3\%)\) significantly greater than that of orthopedic sports medicine \((7.7\%; p=0.005)\) and neurological surgery \((11.3\%; p=0.009)\); significantly lower than that of general surgery \((36.0\%; p<0.001)\); not significantly different than that of orthopedic surgery \((13.3\%; p=0.106)\).

Ethnic diversity of hand trainees is similar to those of other medical specialty trainees. It has shown a significant linear increase over 17 years and is predicted to grow. There is also a significant linear growth in female representation in hand surgery but it is still lower than that of general surgery.

Limitation to this study is that the surveys were subjective and thus resulted in self-reporting of race and ethnicity. Furthermore, there was a small non-responding population present \((4.4\%)\). Finally, the trainees who switched residencies or dropped out in between residencies were not addressed.
Use of Alternative Childhood Immunization Schedules in King County, WA, USA

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The recent rise in parental vaccine hesitancy has been paralleled by an increase in demand for alternative childhood immunization schedules (ACIS) by parents. However, there are few data regarding the proportion of parents using an ACIS and the predominant characteristics of specific ACIS. These data are essential for determining the safety and efficacy of the immunization practices emerging in the United States.

We sought to determine the prevalence and characteristics of ACIS use in King County, WA. We distributed self-administered surveys to a convenience sample of parents who were ≥18 years old, had a child <2 years old, and had an office visit at one of 5 Puget Sound Pediatric Research Network (PSPRN) practices in King County, WA. These PSPRN practices included 34 pediatric providers who routinely recommend the Centers for Disease Control (CDC) immunization schedule. Parents were asked to select one of 4 responses regarding the immunization schedule they planned to use or were using: 1) the schedule recommended by their child’s doctor, 2) the schedule recommended by the CDC, 3) an ACIS, 4) or none. Parents who selected an ACIS were asked to provide the main characteristics of that schedule and its information source. We used Pearson’s χ2 statistic and multivariate logistic regression to test the association of our primary outcome variable (use of an ACIS) with parent demographics.

We received 517 surveys and included 502 in analysis. Most parent respondents were white, ≥30 years old, married, and had a household income >$75,000. The percentage of parents who were using or were planning to use an ACIS was 9.4% (95% CI: 7%, 12.2%). Parents who were white, had a household income of >$75,000, and had a child 12 – 24 months old were more likely to use or plan to use an ACIS than non-white parents (p<.001), parents with incomes ≤$75,000 (p=.007), and parents with children <12 months old (p=.01). In multivariate models that included all demographics, the association between use of ACIS and white parents (p=.001) and parents with children 12 – 24 months old (p=.03) remained significant. Among parents who used or planned to use an ACIS, the most common characteristic of the ACIS was spreading out vaccines (55%). Only 6% described their ACIS as the Dr. Sears’ Alternative Vaccine Schedule, although the book in which it is featured, The Vaccine Book by Dr. Sears, was the most frequently cited ACIS information source (29%).
Characterizing the Signaling Pathway Dependency of Basal-like Breast Cancer

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Molecularly targeted therapy has yielded clinical benefits for many patients with breast cancer. However, patients diagnosed with basal-like breast cancer (BBC), an aggressive molecular subtype usually lacking estrogen and progesterone receptors have poorer outcomes, and molecular targets for drug inhibition have proven elusive. Identification of a molecular target and development of a corresponding small molecule inhibitor could have a profound clinical impact for these patients.

Among the challenges in identifying druggable targets in BBC is that the signaling pathways that BBC cells depend upon for proliferation and survival are poorly characterized. Recent work has found that PI(3)K pathway activation is associated with BBC, particularly via loss of PTEN, making the PI(3)K pathway a potential drug target. The PI(3)K pathway, which regulates many cellular processes such as proliferation and survival, is commonly mutated in breast cancer. PTEN is a phosphatase that inhibits this pathway; accordingly, loss of PTEN is a mechanism by which cancer cells may constitutively activate the PI(3)K pathway to promote growth and survival. We hypothesized that inhibition of the PI(3)K pathway would halt proliferation in BBC with loss of PTEN.

To test this hypothesis, we inhibited several important signaling kinases in this pathway, including PI(3)K, Akt, and mTOR in both BBC cells and luminal cancer cells and monitored both the effect of the inhibitor on cell proliferation and the efficacy of the inhibitor to halt phosphorylation of each kinase’s target. As expected, BBC cells with low PTEN expression had relatively high activation of Akt, suggesting activation of the PI(3)K pathway. To evaluate the efficacy of the drug in inhibiting their respective targets, we used western blotting for phosphorylation of the downstream targets of each kinase and found that each inhibitor succeeded in inhibiting their respective targets. To quantify the effect of the inhibitors on cell proliferation, we used crystal violet staining following drug treatment. We found that compared to luminal cancer lines, BBC cells were resistant to growth inhibition of the Akt/PI(3)K/mTOR pathway. This finding suggests that even though the inhibitors succeeded in inhibiting the kinases in the PI(3)K pathway, they did not block the growth of these lines. However, it is possible that other pathways are compensating for PI(3)K pathway inhibition, which is a common mechanism in cancer for drug resistance. Future work will involve identification and inhibition of other signaling pathways that the BBC subtype is dependent upon for proliferation.
A Validation of Catheter Segmentation for MR-guided Gynecologic Cancer Brachytherapy

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Gynecologic malignancies, including cervical, endometrial, ovarian, vaginal and vulvar cancers, cause significant mortality in women worldwide. In the United States, the number of gynecologic cancers has been increasing in recent years. The standard care for gynecologic cancers involves chemoradiation (concurrent chemotherapy and external-beam radiation) followed by brachytherapy. In contrast to external-beam radiation treatment, in which a linear accelerator aims radiation beams at the pelvis from outside the body, in high dose rate brachytherapy, sources that deliver high doses of radiation are placed directly inside the cancerous tissue using interstitial applicators and catheters.

Many centers employ CT for brachytherapy treatment planning because this imaging modality allows for optimal catheter visualization. However, physicians at the National Center for Image Guided Therapy use high-field MRI for treatment planning, applicator insertion, and catheter placement. Compared to CT, MRI may allow for more precise treatment of the tumor and a reduction in the radiation dose to healthy tissue owing to its increased tumor-to-normal-tissue contrast. Physicians face many challenges with MRI, one of which is catheter visualization. Due to magnetic susceptibility artifacts and the steep brachytherapy dose gradients, catheter identification errors can lead to major dose deviations in targets and organs-at-risk.

The aim of this project was to present a catheter segmentation method for use with 3T MR-guided brachytherapy and validate its results on a phantom and in clinical cases. We report a novel image-processing method (iGyne) for catheter segmentation that extends the distal catheter tip, interactively provided by the physician, to its proximal end, using catheter geometry and appearance in MRI.

Comparisons were performed between results of iGyne and expert human segmentations on phantom and patient MRI. In phantom experiments, the maximum disagreement between automatic and manual MR segmentation, as computed using the Hausdorff distance (HD), was 1.5 mm, which is the same order as the MR image spatial resolution. The disagreement between automatic segmentation of MR images and “the ground truth” (which is manual segmentation of CT images) was 3.5mm.

The segmentation method was then applied to 10 interstitial brachytherapy patients, which included a total of 101 catheters. Compared with manual segmentations, the automatic method correctly segmented 93 out of 101 catheters, at an average rate of 0.3 seconds per catheter (correct defined as HD<2mm, which is the catheter diameter). These results suggest that the speed and accuracy of the proposed catheter segmentation method allow for technical and clinical feasibility. Future directions will compare patient MRI and CT to determine target doses and dosages to organs-at-risk. If, according to published guidelines, the MR-based dose is a significant improvement over CT, then a case will be made for performing MR-based treatments instead of CT.
Civil Society Participation in HIV Policy: A Case Study in Malawi

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Since Malawi’s transition to democracy in 1994, civil society has flourished, including organizations focused on health advocacy. Civil society organizations (CSOs) focused on HIV include networks of people living with HIV, AIDS service providers, other marginalized populations such as men who have sex with men, and international non-governmental organizations. These CSOs typically engage in national budget advocacy, other specific policy issues such as mandatory testing legislation, and preventing stock-outs by alerting officials and the media. They have occasionally directed their attention towards international donors, but have had little interaction with the United States’ President’s Emergency Plan for AIDS Relief (PEPFAR).

PEPFAR has been active in Malawi since 2004 and is one of the largest health sector donors in the country, distributing over $70 million annually. Generally, PEPFAR-Malawi contracts with nongovernmental organizations to provide services. Although in its early years the PEPFAR program was perceived as focusing on Washington-determined priorities, PEPFAR-Malawi was one of the first PEPFAR country teams to develop a Partnership Framework, defining its local role in consultation with the Malawi Ministry of Health. PEPFAR maintains a positive relationship with the government, but its grant recipients remain primarily American, and it has historically had no engagement with local CSOs such as the groups studied.

Through focused interviews with representatives of Malawi CSOs and other organizations, I explored civil society perspectives on PEPFAR. I identified what they believed were PEPFAR’s primary shortcomings. I then consulted with these organizations to develop recommendations for PEPFAR’s 2013 Country Operational Plan (COP) process and the upcoming renewal of their Partnership Framework.

In general, CSOs hope to see PEPFAR engage more substantively in Malawi’s HIV treatment program. First, civil society representatives expressed concern over antiretroviral procurement. Though supported by the Global Fund, Malawi is at recurrent risk of ARV stock-outs and underfunding. Activists called on PEPFAR to serve as an ARV “watchdog,” ensuring sufficient drug stocks and an uninterrupted funding stream. Second, activists identified other challenges in HIV treatment. Among these were health workforce constraints, other commodity shortages, and insufficient resources to treat sero-discordant couples. These could be addressed by PEPFAR through clinician training and recruitment, commodity procurement, and system-wide support. Third, PEPFAR was described as non-transparent. Advocates recommended that PEPFAR engage civil society directly through regular consultative meetings; offering civil society groups decision-making power in the COP and Partnership Framework drafting; and forming alliances on crucial legislative issues such as preventing mandatory testing.
Association and validation of Google Trends data and cancer incidence in the United States from 2004 to 2009: the predictive power of search engine data

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Modern search engine data provides an as-yet untapped source of rich user and patient data regarding health consciousness, behaviors, disease patterns, and more. To date, no study has assessed the utility of Google Trends data in predicting cancer incidences in the United States. Available cancer incidence data from SEER and the CDC are typically one year or more behind the present year, for any given year. However, Google search data is up-dated constantly, passively collected, and is low-cost, allowing for immediate trend analysis. Google data has shown utility in areas such as infectious disease, but non-communicable diseases remain an area of curiosity.

We hypothesized that search query data could model future cancer incidence for a given state. Using data from 2004-2009 for each U.S. state, search volume indices (SVIs) for search queries were taken from Google Trends and age-adjusted cancer incidence rates were taken from the CDC. An exploratory, preliminary analysis was performed to validate Google Trends data and create a predictive model for cancer incidences. Among the search-queries explored, here we highlight the CDC category “all cancer types combined” and the Google search term “cancer” without Boolean operators. Least-squares linear regression was performed for each of the years 2004-2009 to assess correspondence. Iterative modeling was then performed with variables such as SVIs, state population, state computer users, and others.

For 2004-2009, states’ SVIs for the search term “cancer” were well-correlated with the overall age-adjusted incidence rate ($p < 0.01$) for each year. Step-wise regression modeling yielded the following formula to predict a state’s age-adjusted cancer incidence rate for a given year: 

$$(\text{predicted incidence rate}_{year}) = (\text{SVI}_{year-1}) f(\beta_x) + (\text{population}_{year} - \text{population}_{year-1}) f(\beta_y).$$

The functions $f(\beta_x)$ and $f(\beta_y)$ are linear-fitted equations of previous year’s beta coefficients to predict $\beta_x$ and $\beta_y$ for the given year.

The current results suggest that, for a given state, Google Trends SVIs for “cancer” correspond well to CDC total cancer incidence rates and can be used to predict a future year’s total cancer incidence rate. We acknowledge a number of limitations in the study. Conceptually, the generally slower and insidious onset of cancer suggests this application may not be as useful as seen with communicable diseases. Furthermore, the limited available Google data reveals only short-term trends and future studies are necessary to confirm this model as one that is robust.
Developing a Clinical Suicide Prevention Toolbox for Partners In Health in Haiti

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Neuropsychological diseases are the greatest contributors to years lost to disability worldwide, yet over a billion people live in countries like Haiti, where less than 1% of the total health budget is spent on mental health and as much as 85% of those in need of care fail to receive it. As the global health organizations Partners In Health and Zanmi Lasante re-prioritize their primary care service delivery packages, an essential component is implementation of clear practices for assessment and management of suicidality, especially since as much as 20% of some rural Haitian subpopulations endorses current suicidal ideation (SI).

In the spring of 2013, I conducted a literature review and drafted a prototype Toolbox comprised of a screening instrument, a triage protocol, and treatment guidelines for suicidality. I then spent seven weeks in Haiti's Central Plateau and Artibonite Valley, conducting a formative evaluation of SI management. I initially sought to understand current practices of Haitian mental health care providers, structures determining their capacities, their views on SI and best practices, and their responses to my Toolbox. I used interviews, log review, and participant-observation to generate qualitative and quantitative data. Preliminary analyses were performed to facilitate iterative revision of the Toolbox.

Analysis is ongoing, but the data suggested a number of factors that have been incorporated into the Toolbox, resulting in a highly relevant and streamlined deliverable. Most providers were satisfied with the applicability of their training in Interpersonal Therapy for the treatment of depression, emphasizing the importance of family in rural Haiti, and the related need for stigma reduction. Many stated that individuals with chronic diseases require more unique screening and management. Others identified the loss of hope in their patients as incredibly prognostic, and some identified distinct behaviors indicative of changes in hopefulness. In addition to adding to the scant body of knowledge on Haitian mental health, this could contribute to the continued scale-up of contextually-atuned care in Haiti, and it could serve as a model for future work by other students.

While these results are promising, I was limited by my language ability and relied upon interpretation. I was also limited by inconsistent availability of clinical data, though this is improving. Still, it is clear that this approach was able to generate clinically useful results via the combination of (a) semi-structured local engagements with providers and (b) robust organization-level coordination and collaboration that facilitated efficiency.
The Role of MicroRNAs in Vascular Transdifferentiation and Re-Endothelialization

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The coating of anti-mitotic agents onto drug eluting stents (DES) has led to dramatic reductions in neointimal hyperplasia. Unfortunately, patients with DES stents remain on long-term antiplatelet therapy to prevent late thrombosis. Accumulating evidence suggests that these thromboses arise from inadequate re-endothelialization in the aftermath of DES stent placement. Identifying ways to facilitate re-endothelialization while also preventing neointimal hyperplasia are of considerable interest.

MicroRNAs are 22nt long non-coding segments of RNA which regulate gene silencing through translational repression and target mRNA degradation. Among their many functions, miRNAs have been found to regulate cardiovascular processes ranging from angiogenesis to atherogenesis. Recent evidence has implicated miRNAs in regulating the transdifferentiation and reprogramming of different vascular cell lineages.

In this study we aimed to: (1) Identify candidate miRNAs involved in transdifferentiating various vascular cell types into vascular endothelial cells; (2) Assess the role of candidate miRNAs in inducing endothelial phenotypes with in vitro studies; (3) Explore the potential therapeutic role of candidate miRNAs in mouse in vivo studies; and (4) Understand the underlying mechanism for how miRNAs regulate vascular transdifferentiation and re-endothelialization.

Five candidate miRNAs were investigated: mir-143, mir-145, mir-126, mir-146a, and mir-181b. Coronary artery smooth muscle cells transfected with combinations of candidate mimics (mir-126, -146a, -181b) or candidate antagomiR inhibitors (mir-143, -145) were transdifferentiated for 12 days. Cells transfected with the combination of antagomiR-145 and mimics-146a and -181b displayed an endothelial-like phenotype based on: (1) morphological changes; (2) expression analyses on the mRNA and protein levels showing increased endothelial marker expression (KDR, Tie2, eNOS, and vWF) and decreased smooth muscle cell marker expression (SMC-alpha actin, calponin, and MYH11); and (3) functional studies demonstrating enhanced network tube formation and migration in response to VEGF. The conditioned medium from the transdifferentiated cells also increased endothelial network tube formation, migration, and wound closure, suggesting a paracrine role for these transdifferentiated cells in promoting re-endothelialization. Current experiments will elucidate the functional properties of these candidate miRNA when also transfected directly into endothelial cells. Finally, mouse experiments are underway to investigate the therapeutic role of these candidate miRNA in mice in response to carotid artery endothelial denudation by thermal injury.

Taken together, the identified cassette of candidate miRNAs may increase re-endothelialization when transfected into vascular smooth muscle cells both directly via transdifferentiation to an endothelial phenotype and indirectly through pro-angiogenic paracrine effects. These miRNA may introduce novel therapeutic techniques for re-endothelialization and preventing late thrombosis in DES.
Exploring task shifting as a practical framework to promote the delivery of fluoride varnish by non-dental providers in the Region of the Americas

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Early Childhood Caries (ECC) is a chronic, infections, multifactorial disease, defined as the presence of one or more decayed, missing (due to caries) or filled tooth surfaces in any primary tooth in a preschool-age child between birth and six years. In addition to causing pain and suffering, ECC’s are associated with poorer performance in school, lower quality of life, and increased risk of caries in permanent teeth and other health problems. National oral health surveys show that ECC is highly prevalent and severe across the Americas and is an especially severe problem in low-income, rural, and ethnic minority populations. Myriad factors contribute to widespread disparities in oral health, such as cost, access to dental care, and shortage of dental providers.

Fluoride has been shown to be a safe and cost-effective public health intervention to prevent caries. It can be delivered through a variety of means, including community water supplies, salt, milk, and toothpaste. Fluoride varnish, a concentrated form of fluoride painted onto the tooth surface, has particular advantages for a community health setting, including speed and ease of application, efficacy, and palatable taste.

The objective of the literature review is to assess whether task shifting is an approach that can be used to backup PAHO’s efforts to increase access to oral disease prevention intervention in communities with extreme shortage of dental personnel. We used PubMed to review the literature on these topics: risk factors and epidemiology of ECCs, efficacy of community fluoride varnish programs, and cases of task shifting, specifically in community settings.

Literature on task shifting, the process whereby specific tasks are moved to health workers with shorter training and fewer qualifications, indicates promise in scaling-up health workforces to reduce labor shortages in the fields of HIV antiretroviral therapy, emergency obstetric surgery, cataracts surgery, and diabetes management. We found fewer instances of task shifting in Latin America.

Several programs that utilize task shifting in the delivery of fluoride varnish to children exist in North America and Europe, six of which were deemed relevant to the review. The most cited examples were fluoride varnish application programs funded by US Medicaid, in which physicians and their staff apply fluoride varnish in over 40 states. Based on the literature, we conclude that task-shifting fluoride varnish to non-dental providers can be appropriately implemented in Latin America and drafted a concept paper with recommendations to support PAHO’s efforts to influence health policy in the Region.
Cervical Cancer Screening and Barriers to Gynecological Care in a Cohort of FTM Patients Accessing Services at an Urban Community Health Center

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It is widely acknowledged that preventive care is associated with saved lives. However, access to culturally sensitive preventive care for lesbian, gay, bisexual, and transgender individuals remains limited, and many barriers to health promotion in LGBT populations persist. There is a particular lack of clinical discussion of practice issues in the primary care of transgender patients that extends to preventive cancer screening.

Although cervical cancer screening guidelines exist for transgender individuals, no studies have documented the rate of Pap smears among transgender patients or explored barriers to adequate screening. We hypothesize there is a disparity in the rates of Papsmears among individuals on the female-to-male (FTM) spectrum and non-trans women seeking care at Fenway Health as well as sociodemographic, medical, and behavioral correlates to inadequate screening among FTM patients.

We launched a retrospective chart review of 325 FTM patients aged ≥21years with cervixes who received primary care at Fenway Health (2006-2012) and a comparison cohort of 325 randomly selected non-trans women who otherwise met the same eligibility criteria. We created an electronic database using REDCap™ to abstract data including Pap pathology reports, demographics, and mental, chronic, and reproductive health histories. Additionally, we performed 32 in-depth interviews with FTM individuals, 3 focus groups with medical providers, and an online survey open to the FTM community as part of a qualitative substudy of the experiences of Paps and gynecological care among FTM patients and medical providers.

We will compare FTM patients who do not meet cervical cancer screening guidelines to those who do and identify sociodemographic, medical, and behavioral correlates of inadequate screening. Among FTM patients who meet screening guidelines, we will examine the distribution of cytological abnormalities, inadequate samples, and STIs, alongside behavioral risk factors. The non-trans cohort will serve as a “control” to determine if FTM patients are more or less adherent to screening guidelines and whether gender identity is an effect modifier on covariates with nonadherence. Interviews will be transcribed and entered into qualitative data analysis software. A grounded theory approach will be used to code transcripts and develop theory to contextualize the quantitative findings of the chart review.

Initial analyses confirm lower rates of Pap smears and higher rates of inadequate samples in FTM versus non-trans patients. Completion of the chart review and qualitative analysis will identify barriers correlating with these disparities and explanatory models for the prevalence of inadequate Pap samples among FTM patients.
Characterizing the Genetic Profile of Non Small Cell Lung Cancer of Young Patients

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Identification of oncogenes associated with non-small-cell lung cancer (NSCLC) has proved critical for generating novel therapeutic targets and facilitating the application of personalized molecular therapies. Genetic analysis of patients with NSCLC has yielded a number of clinically significant oncogenes, such as EGFR mutants. However, genetic studies of NSCLC have failed to distinguish between NSCLC that presents at an early age and NSCLC that presents later in life. Linkage studies of familial NSCLC reveal that the risk of developing lung cancer at a young age is significantly heritable. Specific genetic alterations such as the EML4-ALK fusion oncogene are enriched in younger NSCLC populations. These data suggest the potential existence of distinctive genetic contributors to lung cancer in young patients. This study was based on the hypothesis that genomic analysis of young lung cancers, especially never/light smokers, presents an opportunity to discover unidentified oncogenic alterations underlying cancer biology.

Two approaches were used to analyze the genetic profile of young NSCLC patients. The first approach was a statistical analysis of eligible NSCLC patients within the Dana Farber thoracic oncology database to determine whether this unique subpopulation of patients was enriched for targetable mutations. Results of this statistical analysis are pending.

The second approach involved a focused genetic analysis of thirteen young NSCLC tumor biopsy samples from eligible patients under the age of 40 with the aim of detecting novel genetic alterations. These samples all lacked the common NSCLC alterations in EGFR, KRAS, ALK, BRAF, HER2 and ROS1. Targeted Next Generation Sequencing was conducted on these biopsy samples by the Center for Cancer Genome Discovery. The resulting sequences were examined for alterations in genes known to harbor oncogenic rearrangements as well as for point mutations that could represent potential driver mutations. One potential alteration was discovered in an intron within the ROS gene. The functions of the genes containing novel point mutations for each of the wild type biopsies were analyzed to determine which genes could serve as driver mutations. Unlikely driver mutations based on factors such as SNP frequency and tissue fraction were removed from consideration. Identified point mutations within genes of interest, ranging from one to ten per sample, require further validation via functional studies.

While these two approaches have yet to yield conclusive results, the comprehensive sequencing approach has identified several novel point mutations that could represent oncogenic alterations.
Correlation Structure of Interspike Intervals in Conductance-based Neuron Models with Adaptation

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Information processing and signal transmission by single neurons is poorly understood theoretically in the presence of noise and adaptation. An important step in understanding is the statistical characterization of the neural spike patterns. Experimental evidence suggests that interspike intervals (ISI) of neurons with adaptation are not independent; rather, they correlate over a few lags. This requires the use of non-renewal neuron models to explain neural spike train statistics.

Recent advances using simplified neuron models through the integrate-and-fire framework describe the nonlinear adaptive spike mechanism, allowing for analytical formulas for spiking statistics. However, several quantitative predictions for correlation patterns do not explicitly depend on this framework, which suggests that the derived formulas may also be applicable to more biologically realistic neuron models.

The current study investigates if the Traub-Miles model, a biophysically realistic and detailed conductance-based, Hodgkin-Huxley-type neuron model with an M-type adaptation current, predicts correlation patterns congruent to the integrate-and-fire models. We hypothesized that the model would corroborate the tight relationship between interval correlation in spike trains and nonlinear neural dynamics in the presence of adaptation.

The model was implemented using the C programming language and MATLAB to simulate the stochastic model for different parameters to determine ISI statistics. ISI distribution statistics corroborated the validity of the model.

Simulation results were compared to theory using the phase-response curve (PRC), which was computed numerically from the deterministic model using the perturbation method. The PRCs showed type II behavior consistent with the observed positive correlations. Furthermore, the theory depends on the adaptation strength, which needs to be estimated from the maximal conductance mediating the M-type adaptation current. Initial results were unclear in assessing the agreement between theory and simulation, likely because correctly extracting the adaptation strength in the integrate-and-fire model from the corresponding conductance in the Traub-Miles model is complex.

To further elucidate the relationship between theory and simulation, next steps include a detailed parameter study to better understand ISI correlation patterns in relation to the PRC. Conversely, through using the correlation patterns, adaptation time-scale and conductance can be measured.

Through the work, further elucidating spike correlations could yield valuable insights into neural biophysics and towards a greater understanding of neural signal transmission.
Global Modification to the WHO Surgical Safety Checklist

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Over 50% of adverse events in hospitals affect surgical patients. In 2008, the World Health Organization (WHO) published the Surgical Safety Checklist to reduce surgical errors resulting from poor communication and teamwork amongst surgical teams. Since its publication, over 4,000 hospitals have adopted the WHO Surgical Safety Checklist. To foster checklist ownership and facilitate use, hospitals are encouraged to modify checklists, but to preserve teamwork checklist items.

This study aimed to understand how hospitals have modified the checklist globally. Items retained or removed can provide insight into how hospitals value particular checklist items. Developing an understanding of modification can guide future implementation efforts and design of updated versions of the WHO checklist.

126 checklists were studied from 37 countries and 19 US states. Checklists were analyzed based on whether they added or removed checklist items. Checklists were also provided a teamwork score based on how many communication items were retained from the original WHO checklist. Checklists modifications were aggregated and analyzed geographically.

Modified checklists contained more total items than the original WHO checklist, averaging 33.5 items versus 28. The most commonly added items were procedural, not teamwork-based: implant availability, DVT prophylaxis, and patient positioning. 50% of all checklists removed two or more of the original seven teamwork items. Surgeon-led items were also more likely to be removed when compared to anesthetist-led and nurse-led items. This observation of longer checklists, fewer teamwork items, and fewer surgeon-led items was more profound for US checklists. The average number of teamwork items on US checklists was significantly lower than on non-US checklists (3.98 vs. 5.64, p<0.05). US checklists were also more likely to eliminate all surgeon-led items (21.4% of US vs. 12.7% of all checklists).

Checklists should strike a balance between critical items and teamwork checks, meanwhile ensuring the checklist is feasible in length. The observation that 50% of all checklists removed at least two teamwork items, but that 5.5 critical checks were added on average is concerning. Hospitals, while eager to add items, are primarily adding procedural checks, but not necessarily preserving essential teamwork and surgeon-led items. We recommend hospitals preserve all teamwork and surgeon-led items, but limit checklist length to ensure feasibility. Hospitals should devise a mechanism to review checklists periodically and ensure revisions are made to reflect this essential balance between reviewing critical steps and promoting teamwork.
The Effect of Mandibular Advancement and Bite Opening on Upper Airway Cross-Sectional Area in an Obstructive Sleep Apnea Patient and a Normal Patient

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Obstructive sleep apnea (OSA) is a common sleep disorder characterized by repeated episodes of upper-airway collapse, and is associated with long-term adverse health consequences. Continuous positive airway pressure is an efficacious treatment, but is poorly tolerated. As an alternative, mandibular advancement devices (MADs), which improve airway patency by increasing upper-airway cross-sectional area (CSA), are becoming frequently utilized. Despite this widespread use, a number of patients who use these devices do not have their OSA resolved and in some cases the devices even worsen OSA severity. This finding may be related to the fact that the optimal device design that most effectively improves upper-airway CSA has not been studied. Two properties can be modulated in MAD design: the level of mandibular advancement and the degree of bite opening. Therefore, we aimed to examine the effects of adjusting the degree of mandibular advancement and bite opening on the CSA of the upper-airway in subjects with and without OSA.

In 6 healthy controls and an OSA patient, MRI of the upper-airway was performed during wakefulness in a supine position with and without MADs. Ten MADs were used with various combinations of mandibular advancement [0,3,6mm] and bite opening [0,4,8mm]. Changes in the CSA of the upper-airway (retropalatal region) were analyzed using the three-dimensional imaging software AMIRA for each MAD.

To date, we have analyzed one control and one OSA patient. In the control, the greatest percent increase in retropalatal CSA (232.9±30.2% relative to a 100% baseline) was achieved with the largest degree of mandibular advancement (6mm) and bite opening (8mm). By contrast, none of the MADs substantially increased the retropalatal CSA in the OSA patient. Surprisingly, several MADs decreased the upper–airway CSA, with the largest decreases occurring at 0mm advancement and bite opening in the control (62.6±11.4% of baseline CSA) and 0mm advancement and 3mm bite opening in the OSA patient (80.3±13.4% of baseline CSA).

Our preliminary results suggest that MADs have a variable effect, both within and between individuals, on improving upper-airway dimensions. This variability may be a key reason certain MADs do not always effectively treat OSA. Based on the lack of improved CSA with any MAD in the OSA patient studied, we predict that a MAD would be unlikely to resolve their OSA. Future research is needed to determine who is likely to benefit from MADs and whether there is a single device design that is optimal for all patients.
Determining Factors of Oral Hygiene Behavior (OHB): How oral health knowledge, perception of costs and the Theory of Planned Behavior

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Oral hygiene behavior (OHB) is intimately linked to oral health. Without a proper regimen of self-driven dental care, persons can develop oral infections that will cause significant pain and discomfort, which could ultimately lead to the preventable loss of natural teeth - consequences which all negatively impact oral function and overall quality of life. Additionally, these infections may have implications beyond the scope of the oral cavity. Studies show a growing body of evidence that state that there is an association between oral infections and coronary heart disease, the most common type of heart disease. In order to intervene and adjust OHB to improve patient quality of life, as well as reduce risks to overall health, it is instrumental to first understand why behaviors exists in their current form.

Past studies have shown that attitudes (ATT), subjective norms (SN), and perceived behavioral controls (PBC) are major determinants of OHB. These three elements comprise the variables of the Theory of Planned Behavior (TPB), an explanatory model of behavior used in a wide variety of studies across many disciplines. Although work has been done establishing the links between OHB and TPB, many of these studies examined the intentions of individuals to perform certain behaviors rather than the performances of the actions themselves, or they used an incomplete measure of performed OHB.

Through the use of a survey that utilizes a newly created and verified index which measures performed OHB, this study explores the relationship between attitude, subjective norm, perceived behavioral control and performed OHB, while also examining the relationship between performed OHB, oral health knowledge (OHK) and perceived future financial impact (PFFI) - an individual's perception of future costs associated with poor OHB.

Surveys were administered to people in the waiting rooms of three private dental practices and the dental clinic of York Hospital in York, Pennsylvania. To date, 480 surveys have been collected and administration is ongoing. Once all data are collected, an OHB index score will be calculated for each participant. Cronbach's alpha, range, mean and standard deviation will be calculated for the primary variables (ATT, SN, PBC, PFFI). Linear regression of OHB on ATT, SN, PBC, OHK, and PFFI data will be analyzed to search for associations. Pearson's correlations between OHB and the primary variables will also be performed.
Vitamin D3 Intervention Modifies the Relationship between the Renin-Angiotensin-Aldosterone System and Parathyroid Hormone in Humans

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Observational studies suggest a positive relationship between aldosterone and parathyroid hormone (PTH) in the pathophysiology of primary hyperaldosteronism (PA). The relationship between PTH and the renin-angiotensin-aldosterone system (RAAS) in normal physiology needs clarification. We evaluated the normal physiologic relationship between the RAAS and PTH using interventional study protocols in humans without PA. In controlled clinical research settings, we investigated: 1) The PTH-response to acute RAAS stimulation and acute RAAS inhibition, before and after 4 weeks of high-dose vitamin D3 therapy (450,000 IU); and 2) The PTH-response to 6 weeks of blinded randomization to spironolactone or placebo (n=27). Prior to the vitamin D3 intervention, an angiotensin II (AngII) infusion acutely increased PTH (+10.3%), while captopril acutely decreased PTH (-9.7%) and enhanced the PTH-response to a subsequent AngII infusion (+16.0%) (P<0.01). Following vitamin D3 therapy, the acute PTH-response to AngII was further increased (+26.4%) while the PTH-response to captopril was decreased (-6.8%). Chronic spironolactone therapy did not influence PTH in our population without PA. These interventional protocols uncovered a key physiologic relationship whereby acute RAAS stimulation raised PTH and acute RAAS inhibition lowered PTH. The magnitude of these interactions was modified by vitamin D3 therapy and by ACE inhibition. Such advances in the understanding of the normal physiologic relationships between the RAAS, PTH, and vitamin D status may improve the understanding and treatment of pathologic conditions involving the RAAS and PTH.
Characterizing adventitial inflammatory infiltrates in human atherosclerotic coronary arteries

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The clinical manifestations of atherosclerosis are leading causes of morbidity and mortality in the United States. Much of the cellular biology of atherosclerosis, including the impact of inflammation, has been elucidated, but the role of adventitial cells in modulating the progression of atherosclerosis is unclear.

Immune cells have long been observed in the adventitia of human and murine arteries at the site of atherosclerotic plaques, but their structural organization has not been fully characterized. In murine aortas in the setting of advanced atherosclerotic disease, studies have shown that these adventitial infiltrates can organize to form tertiary lymphoid organs (TLOs), and speculations have been made about the contribution of T lymphocyte-B lymphocyte collaboration in lesion development. Although it is possible that TLOs might be present in the development of atherosclerotic disease in humans, no study has conclusively characterized such substantive lymphoid infiltrates in human coronary arteries. We hypothesized that adventitial lymphocytic infiltrates would be present in a majority of atherosclerotic coronary arteries but would not exhibit the organizational characteristics necessary for categorization as a TLO.

To test this, we collected 311 histological slides of coronary artery cross sections from 112 autopsy cases from the Department of Pathology at the Brigham and Women’s Hospital. Using images of the slides scanned by the Longwood Specialized Histopathology Services, we analyzed 575 cross sections from these 112 patient cases. A total of 175 sections from 42 cases showed adventitial lymphocytic infiltrates. We subsequently staged the cross sections containing infiltrates on a 1-4 scale of ascending size. In total, 4.5% of cases with infiltrates scored as a class four, 44% scored as class three, 23% scored as class two, and 29% scored as class one. With further assistance from the Longwood Specialized Histopathology Services, we used immunohistochemistry to stain the slides for CD3 and CD20, markers of T and B lymphocytes, respectively. Although complete analysis is pending, initial review reveals that a small minority of cases contain elements of complexity characteristic of TLOs, including separate B and T cell zones. We are currently staining for CD4 (helper T lymphocytes), CD8 (cytotoxic T lymphocytes), Bcl-6 (B cells in germinal centers), and MECA-79 (high endothelial venules).

This data suggests that a small minority of cases contain adventitial infiltrates of appropriate size and complexity to be considered as possible TLOs. Ongoing analysis will further characterize the nature of adventitial infiltrates observed in atherosclerotic human coronary arteries.
Oral Health Status and Risk Factors for Dental Caries in Patients with Autism Spectrum Disorders

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Patients with Autism Spectrum Disorders (ASD) often present with several behavioral impairments, which can lead to difficulty in maintaining oral health. Therefore, patients with ASD are considered to be at an increased risk of caries. Several studies have shown that children with ASD are more susceptible to caries and have more difficulty maintaining oral care, however, there is limited comprehensive data on the impact of dental related behavioral issues on oral health. ASD patients may have higher risk of oral health issues such as bruxism, self-injury and malocclusion. By assessing specific oral health outcomes this study aims to provide insight into the needs of ASD patients and determine which aspects of oral health are most affected by clinically significant behavioral problems.

The study is designed as a retrospective chart study of patients ages 3 to 18 with a diagnosis of ASD who have been seen at both the Developmental Medicine Center and the Dental Clinic at Boston Children’s hospital. We constructed a data abstraction form to gather data from patient records regarding cognitive functioning, behavioral problems, as well as specific oral health outcomes including presence of caries, frequency of snacking, and frequency of brushing. Analysis of the collected data will include logistic regression models and also Chi-squared analysis for binary variables performed.

One of the limitations of this study is that comprehensive data is not available for every patient since records were transferred from paper to electronic in the recent past. Further, the dental charting methods were recently standardized and therefore, data collected prior to this standardization may limit the comprehensiveness of some of the data.

To date, the abstraction form has been completed and IRB approval has been granted and data collection is in process. Data collection will be completed by December 2013 and analysis will occur at the beginning of 2014.
Lifestyle intervention among overweight and obese schoolchildren: pre-intervention analysis of experimental study in Sousse, Tunisia

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Tunisia is experiencing an epidemiological transition where the population is engaging in a more sedentary lifestyle and eating less healthful foods. Consequently, rates of overweight and obesity in children are increasing. According to the WHO, 21.5% of boys and 25.1% of girls in Tunisia are either overweight or obese. It is crucial to acknowledge this trend and implement a healthy lifestyle intervention programs in schools in order to reduce the amount of overweight and obese children.

A school-based intervention is the best way to address this problem. Based on data from various school based intervention programs, Silveira et al (2011) found that school-based interventions were the more effective approach when they lasted longer than one year, introduced physical activity and nutritional education into the regular curriculum, and had parental involvement.

The goal of this initiative is to understand how to reduce overweight and obesity among school age children in Sousse, Tunisia, specifically by evaluating the effects of a one year intervention program in schools in Sousse and Msaken. The central hypothesis is that this one year intervention will increase the proportion of school children who follow a balanced diet and are regularly active and decrease the mean body mass index z-score by 0.2. Specifically, the aim of my project was to analyze pre-intervention data.

Data was collected from 733 school children ages 14 to 16 from eight schools in Sousse and seven schools in Msaken. Sex, height, weight, date of birth, glucose, HDL, LDL, total cholesterol, and triglycerides were collected and inputted into SPSS. From these measures, the following variables were calculated: age in months, BMI, BMI z-score, and classification into overweight (BMI 25 or greater), obese (BMI 30 or greater), or morbidly obese (BMI 40 or greater).

These data indicate that 58%, 21%, and 21% of the children were overweight, obese, and morbidly obese, respectively. Chi-Square analysis indicates that female children had a significantly higher BMI than male children of the same age (2 df= 6.601, p=0.037). Morbidly obese children have higher triglyceride levels and lower HDL levels compared to obese and non-obese children. Obese children and morbidly obese children have a higher average LDL level compared to non-obese children. The data also indicate that children who were older than average in their respective grade levels had a higher BMI than children who were within average age limits. Total cholesterol, HDL, and triglycerides were significantly different between schools.
The Role of β1 Integrins in Mediating CD8+ T-Cell Homing to Skin Following Viral Skin Infection

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Recent work with vaccinia virus (VACV) has demonstrated that cutaneous viral infection generates a stable population of CD8+ T-cells with a CD44+ CD62L- phenotype that deploy most abundantly to the infected skin. These cells are also abundant in normal skin and detectable in peripheral organs, which include gut, lung, and liver. Unlike classical central memory T-cells (T_{CM}) and effector memory T-cells (T_{EM}), these CD8+ CD44+ CD62L- resident memory T-cells (T_{RM}) stably colonize the skin, do not appear to re-circulate in the blood, and provide long-term protection against pathogen re-exposure. To date, however, the precise factors that mediate the migration and retention of T_{RM} cells to skin tissue have not been fully elucidated.

Integrins are transmembrane cellular receptors that mediate cell-matrix and cell-cell adhesion. In particular, β1 integrin is ubiquitously expressed in all cell types except erythrocytes, and has been shown to interact with a variety of different β integrins to mediate cell adhesion and migration. Given the important function of β1 integrins in cellular adhesion in other T-cell types, we hypothesize that these integrins may also play a role in the migration and retention of T_{RM} cells to the skin.

In naïve mice, very few T-cells with a T_{RM}-like phenotype (CD44+ CD62L-) were found in the CD8+ population in the spleen, skin-draining lymph nodes, and skin (2%, 1.8%, and 17.9%, respectively). Following VACV infection, however, the T_{RM} subpopulation was significantly upregulated in these organs at both the acute phase of infection (Day 7) (33.4%, 5.0%, and 49.2% respectively) and the memory phase of infection (Day 30) (30.3%, 19.1%, and 88.3%, respectively). Furthermore, β1 integrin expression was significantly upregulated in cells with a T_{RM}-like phenotype following VACV infection compared to cells with a T_{CM}-like phenotype or naïve T-cells. In the T_{RM} subpopulation, the percentage of T-cells that expressed β1 integrin increased dramatically in infected mice at both the acute and memory stages of infection compared to naïve mice (34.5% and 33.2% vs. 2.3% in spleen; 4.68% and 18.4% vs. 0.93% in skin-draining lymph nodes; 51.6% and 79.7% vs. 0% in skin). Interestingly, more than 90% of VACV-specific cells in lymphoid organs and 70% in the skin also expressed β1 integrin. Taken together, these results suggest that β1 integrin plays a role in skin homing of T_{RM} cells following cutaneous infection. Future work will focus on functional studies of the role of β1 integrin in T_{RM} migration and retention in the skin.
Identification of Molecules that Affect Adhesion, Growth, and Volatile Sulfur Compound production of *Porphyromonas gingivalis* and *Fusobacterium nucleatum*

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Periodontal disease is a chronic inflammatory disorder characterized by inflammation of the gingiva with destruction of supportive structure surrounding the tooth. It affects up to 80% of the adult population worldwide with severe cases leading to edentulism. Recent studies have suggested a causative link between periodontal disease and several inflammatory diseases including diabetes, cardiovascular disease, and obesity.

The primary causative agents of periodontal disease are Gram-negative bacteria. Of these, *Porphyromonas gingivalis* plays a significant role due to its ability to inflict damage through mechanisms including promoting its endocytosis into host cells, gingipain proteases, and immunoevasive capsule. As severity of periodontitis is directly associated with numbers of *P. gingivalis* in the host oral flora, treatments that reduce its numbers are highly sought after. Another Gram-negative anaerobe, *Fusobacterium nucleatum*, plays a role in progression of periodontal disease, through promoting colonization of the oral cavity by *P. gingivalis* and other bacteria. Unlike *P. gingivalis*, *F. nucleatum* is found in both healthy and disease states, serving as a major contributor to plaque formation. In addition, *P. gingivalis* and *F. nucleatum* share the ability to produce volatile sulfur compounds (VSCs). These products of bacterial protein breakdown are a cause of halitosis (foul breath odor) and are toxic to host tissues.

To elucidate methods to target these pathogens, we sought to identify compounds that affect any of the following factors: 1) adhesion of *P. gingivalis* to host cells, 2) growth of *P. gingivalis* and *F. nucleatum* and 3) ability of *P. gingivalis* and *F. nucleatum* to produce VSCs. To carry this out, we performed chemical screens with three pre-existing drug databases: FDA-approved drug library, natural inhibitors and compounds library, and a small molecule library. The screens were performed using a 96-well plate format with each compound run in triplicate at a final concentration of 10µM using either water or DMSO as solvent. Growth curves were recorded with measurements taken over a period of 48 hours using a plate reader (OD600nm). At the conclusion of the growth curves, either biofilm assays or VSC assays were performed to assess the effect of compounds on the formation of biofilm or ability to produce VSCs. Though an initial pass of the Natural Compounds Library did not identify any molecules that significantly affect growth, biofilm, or VSC production, further trials are being performed to verify these results. In addition, the remaining chemical libraries will be screened upon completion of this assay.
Hearing the light: a behavioral and neurophysiological comparison of two optogenetic strategies for direct excitation of central auditory pathways

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The auditory brainstem implant (ABI) is the only option to provide hearing for deaf individuals who are not cochlear implant candidates due to absent or damaged cochleae or auditory nerves. However, most ABI users only have sound awareness and no meaningful speech comprehension. Many patients also experience side effects from stimulation of non-auditory neurons.

One explanation for the limitations of the ABI suggests that when multiple electrodes simultaneously stimulate neurons, electrical field interactions disrupt individual waveforms. In contrast, light is less limited by field interactions and can be more easily focused.

Optogenetic technology uses light to control the activity of genetically modified neurons expressing light-gated ion channels, providing a means to manipulate specific neural circuits with temporal and spatial precision. However, most known channelrhodopsins remain unable to reconstruct the submillisecond precision and speed of central auditory representations.

In this study, we compared the standard opsin Channelrhodopsin2 (ChR2) to Chronos, a newly-isolated depolarizing channelrhodopsin that has demonstrated enhanced photosensitivity and faster channel activation kinetics than other existing channelrhodopsins in acute brain slice experiments. We used viral-mediated gene transfer to express ChR2 or Chronos in neurons of the murine inferior colliculus (ICc).

Extracellular in vivo recordings from infected neurons confirmed the differences between ChR2 and Chronos. By delivering optical or acoustic pulse trains at rates from 0-300 Hz, we observed synchronized responses with ChR2 as high as 80 Hz, but rapidly adapting onset-like responses at higher rates. By contrast, neurons infected with Chronos accurately entrained their spike trains to optical stimulation as high as 200 Hz, approximating the synchronization limit for natural acoustic stimulation in the same neurons. Optical stimulation of Chronos at higher rates evoked non-adapting responses as high as 300 Hz, although spikes were no longer synchronized to pulse trains. We also implemented neural decoders using pattern recognition techniques to infer laser pulse rates based on spike responses. Responses from Chronos-infected cells show significantly better discriminability than responses from ChR2-infected cells, especially at higher rates. These results demonstrate that Chronos can transform a wider range of temporal stimulation patterns with higher accuracy compared with ChR2.

Ongoing experiments seek to implant the murine ICc with chronic optical fibers to determine whether the enhanced temporal coding range of Chronos translates into better behavioral discrimination of optogenetic excitation at high rates. These studies advance the potential for optogenetic strategies to improve the auditory implant.
H₂O₂, Autophagy and the mTOR Pathway: is there a Link?

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Many receptor-mediated signaling pathways in vascular endothelium lead to an increase in intracellular levels of hydrogen peroxide (H₂O₂), an oxidant species that may act as a signaling intermediate. The increase can be due to either activation of enzymes that produce H₂O₂ or through the inactivation of enzymes that decompose H₂O₂. The peroxiredoxins (PrxI to PrxVI) are a family of enzymes that degrade H₂O₂, with several different isoforms expressed in endothelial cells. The pathophysiology of reactive oxygen species has been implicated in diseases such as atherosclerosis, but the physiological roles of these transient species are poorly understood. Since Prx is expressed in endothelial cells and since reactive oxygen species such as H₂O₂ are readily produced in the same cells, the two goals of this project were to determine the best conditions for knocking down key Prx enzymes using siRNA methods, and also to study whether or not H₂O₂ modulates growth via the mTOR signaling pathway.

In order to test the hypothesis that Prx isoforms are differentially involved in the modulation of signaling initiated by various agonists, we used isoform-specific duplex siRNA targeting constructs to knock down Prx isoforms in HEK293 cells. We focused on PrxVI because it is known to undergo reversible phosphorylation, and validated a siRNA targeting construct that yielded a ~90% knockdown of PrxVI 48 hours after transfection with no substantive off-target effects, as quantified in immunoblot analyses. Studies of cell signaling pathways modulated by PrxVI are ongoing using cells transfected with control and PrxVI siRNA targeting constructs.

We also studied the role of H₂O₂ in cellular growth by measuring the phosphorylation of p70S6K and pS6, which are phosphoproteins downstream of mTOR. The mTOR protein controls a proliferative pathway that is triggered when growth is needed. Oxidative stress leads to an inhibition of the mTOR pathway. We hypothesized that increasing levels of hydrogen peroxide would lead to a decline in activity of the mTOR pathway as oxidative load increases inside the cell. We generated H₂O₂ using the enzyme glucose oxidase incubated with HEK293 cells. Our preliminary data indicate that H₂O₂ modulates the mTOR pathway, leading to a significant decrease in the phosphorylation of both p70S6K and pS6 with increasing concentrations of H₂O₂. We plan to continue these studies in order to identify the molecular mechanisms by which H₂O₂ modulates the mTOR pathway, including analyses of apoptosis and autophagy.
The Yield of Downstream Tests after Exercise Treadmill Testing: A Prospective Cohort Study

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While advances in cardiovascular imaging have greatly improved our ability to diagnose and treat coronary artery disease (CAD), the rising costs of noninvasive testing have generated concern regarding the potential overutilization of such testing. As the utility of additional cardiac diagnostic testing following exercise treadmill tests (ETT) is not well characterized, the goal of our study was to estimate the frequency and results of downstream testing following ETT.

We followed consecutive individuals without known CAD referred for clinical ETT at a large medical center. We measured the frequency and results of downstream imaging tests and invasive angiography within six months of ETT, and the combined endpoint of survival free from cardiovascular death, myocardial infarction, and coronary revascularization.

Among 3,345 consecutive subjects who were followed for a mean of 2.5±1.1 years, 332 (9.0%) underwent noninvasive imaging while 84 (2.3%) were referred directly to invasive angiography after ETT. The combined endpoint occurred in 76 (2.2%) patients. The annual incidence of the combined endpoint following negative, inconclusive and positive ETT was 0.2%, 1.3% and 12.4% respectively (P<0.001). Rapid recovery of ECG changes during ETT was associated with negative downstream test results and excellent prognosis while typical angina despite negative ECG was associated with positive downstream tests and adverse prognosis (P<0.001). Younger age, female gender, higher METs achieved and rapid recovery of ECG changes were predictors of negative downstream tests.

Given the observational single-center design of our study, these results might be less applicable to other institutions.

Nevertheless, our study demonstrates that among patients referred for additional testing after ETT, the lowest yield was observed among individuals with rapid recovery of ECG changes or negative ETT while the highest yield was observed among those with typical angina despite negative ECG or a positive ETT. These findings may be used to identify patients who are most and least likely to benefit from additional testing.
Defining a Novel Immunohistological Approach for Diagnosing Malignant Melanoma

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Malignant melanoma (MM) is the most deadly of all skin cancers, contributing up to 75% of skin cancer deaths. Current tools available for diagnosing MM include the “ABCDE” criteria and by determining histological features, such as tumor depth, inflammation and number of mitoses in conjunction with immunostaining of melanocytic markers, S100 and Pmel 17. Despite these tools, determining whether melanoma “mimics” are malignant and whether severely-dysplastic nevi will become malignant are still major challenges and could greatly impact treatment decision-making.

In this study, our goal was to establish a novel immunohistological approach that could help distinguish MMs from benign melanocytes. Exciting studies from our group show that galectin-1 (Gal-1), a lectin known for binding T-cell surface glycoprotein ligands and attenuating anti-melanoma responses, can also bind melanoma cell glycoproteins and trigger malignant behavior. Our data also demonstrate that human melanoma cells and not normal melanocytes express a predominance of Gal-1-binding activity on the glycoprotein, melanoma cell adhesion molecule (MCAM), implicating Gal-1-binding MCAM as a marker of MM. Thus, we hypothesized that detecting Gal-1-binding MCAM could help differentiate malignant melanocytes from non-malignant counterparts, offering a new and powerful approach to diagnose MM.

Therefore, we performed dual immunofluorescence (IF) using either anti-MCAM or S100 antibody and a Gal-1–human immunoglobulin (Gal-1hFc) construct to detect Gal-1 ligands. IF analysis was performed under fluorescence microscopy on FFPE-sections of human melanoma cells; MM (n=7), pre-malignant severely-dysplastic nevus, ordinary compound nevi (n=3) and normal skin (n=3). Optimal concentrations of Gal-1hFc and IF antibodies were established using a Gal-1 ligand+MCAM+S100+human A375 melanoma cell line.

In all tissues, IF showed: 1.) strong Gal-1 ligand+staining of pre-malignant and malignant melanocytes, vascular structures and dermal fibrils, 2.) robust S100+staining of normal, pre-malignant and malignant melanocytes and skin-resident DCs, and 3.) strong MCAM+staining of the epidermis and malignant melanocytes. Dual IF with Gal-1hFc and S100 Ab distinguished Gal-1 ligand+S100+ malignant melanoma cells, including early-stage melanoma in situ, from Gal-1 ligand+S100+ benign counterparts. A severely-dysplastic nevus with inflammation, which often preludes malignancy, also exhibited robust dual Gal-1 ligand+S100+staining. However, while dual IF with Gal-1hFc and anti-MCAM Ab was effective for staining deep MMs, staining of epidermal MMs was complicated by fluorescence bleed-through from anti-MCAM Ab staining of keratinocytes. These results implicate dual IF with Gal-1hFc and anti-S100 Ab as a potentially effective method for distinguishing MM, notably early-stage epidermal subsets, from benign mimics.
A Mobile Health Program’s Intervention for Urban Youth

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The Family Van is a mobile health clinic based in Boston that provides preventative health care services to the medically underserved and minority communities by using their “Knowledgeable Neighbor Model”. However, they have not been able to focus specifically on youth (ages 13-24), which is reflected in the low percentage of youth (only 5%) that they have served. Healthy People 2020 and recent Health of Boston reports have identified common health disparities among youth, especially within the communities that the Family Van serves. Therefore, the Family Van identified a need to increase their impact on youth.

The objectives of the Family Van’s youth intervention are to augment the screening priorities for youth, in order to focus the care they receive on the health issues most relevant to youth in the most efficient manner possible, improve methods by which our efforts are evaluated, and to attract more youth to the services of the Family Van, in order to have a wider impact on the youth in the communities we serve.

During the summer of 2012, a comprehensive “Youth Intervention Plan” (YIP) was developed with objectives that would help the Family Van reach its objectives. A literature review, collection of ideas and feedback from community members and youth, and analysis of Family Van data were collected in order to identify the best ways to meet the objectives of the intervention. During the summer of 2013 a “Youth Satisfaction Survey” (YSS) was developed, as well as a “Health Literacy Measure” (HLM), which was developed through use of a literature review and professional consultation.

Although there has not been enough time to evaluate the intervention, measures of success have been identified. First, the clinic already has a “Service Provider Form” (SPF) which keeps track of the demographics of the van’s visitors and the types of services that they receive. Second, the YSS was developed in order to measure the effectiveness of our new marketing campaign and to confirm that our services match the preferences of youth in our communities. Third, the HLM was developed to serve as a measure of the effectiveness of our health interventions on youth.

The Family Van’s youth intervention has only recently been partially implemented due to lack of funding and time restraints. After these problems are solved, a full evaluation of the success of the Family Van to increase its impact on the youth in their communities can ensue.
The role of the thalamus in patterning learned vocalizations

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Human language is a remarkably complex and versatile system of communication which requires precise control and coordination of muscles in the upper vocal tract and respiratory system. This control has two purposes: first, it allows syllables to be formed with the correct pitch, intonation and rhythm. Second, it enables syllables to be produced in the correct sequence to form words. We will investigate how the brain flexibly controls the sequential ordering of vocal elements in speech, because this is a fundamental mechanism by which information is transmitted in language. To examine how syllable sequence is determined in learned vocalizations, we used an established model of vocal learning, the songbird; specifically, the zebra finch (*Taeniopygia guttata*). The songbird has a brainstem-thalamocortical loop, analogous to one in humans, that controls the muscles of the upper respiratory tract and respiratory system. Our studies focused on the thalamic nucleus Uvaeformis (Uva), which projects to cortical areas directly involved in syllable production in song. Behavioral studies have revealed that bilateral lesions of Uva result in a loss of stereotypy in song. The post-lesion songs exhibit no distinct identifiable syllables and have a broad, nearly exponential distribution of syllable durations, which is characteristic of subsong, a juvenile form of birdsong. In addition, chronic recordings in adult birds have revealed that neural activity in Uva peaks 30-40ms prior to syllable onsets. These findings are consistent with the hypothesis that Uva activates avian cortex prior to syllable onsets and initiate syllables that are executed by the cortex.
A Quality Improvement Evaluation of a Pediatric Asthma Medical Home on Care Outcome Measures.

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Asthma is the leading chronic disease among children in the US and is the leading admission diagnosis at Boston Children’s Hospital. High healthcare utilization costs are associated with asthma due to fragmented care, poor patient education about disease management, and the compounding of social and environmental factors that adversely affect patient health.

The objective was to evaluate the impact of a quality improvement multidisciplinary asthma medical home initiative on asthma care and outcomes within the Children’s Hospital Primary Care Center (CHPCC). CHPCC provides care for over 2,000 children with asthma. Many patients are from Boston’s poor inner city neighborhoods with high rates of emergency department (ED) and inpatient visits. The medical home team consisted of intensive management of highest risk patients, including monthly team meetings, embedded social work and patient navigator support, referrals for in-home education support and connections with community resources for unmet social needs. To date, no one has specifically examined the synergistic impact on patient outcomes when interventions are combined in a multidisciplinary medical team approach.

As part of a quality improvement project, we performed a chart review of a subset of patients seen by the multidisciplinary asthma team. Emergency department visits and in-patient admissions were evaluated. Asthma urgent care and preventative visits were examined since these types of visits more routine care and asthma outcomes. All four types of visits were evaluated over a 5- year program period, from 1- year pre-intervention through 2 years-post intervention, from October 2006-October 2011. In phase II, we will conduct an assessment of unmet needs prior to the enrollment of the phase I patients in the asthma medical home. Asthma triggers, unmet social needs, and medication adherence will be evaluated. We will then evaluate how these unmet needs were addressed through the medical home. This allows us to look more deeply at the impact of care process on asthma outcomes.

Preliminary data from a group of 140 high-risk patients managed by the asthma team during the 2007-2011 period demonstrate a 50% reduction in asthma urgent care visits, 71% reduction in asthma ED visits, and 50% reduction in asthma admissions. Our enhanced approach to asthma care, redirecting focus from the encounter-centered provider relationship to a system with broad view of chronic disease management has demonstrated improved health outcomes in our asthma patients. It also supports the need for integrated educational and care coordination to better serve our vulnerable patient populations.
Lifetime Experiences of Violence and Risk of Maternal Pre-Pregnancy Obesity

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Background. We examined the extent to which maternal lifetime experiences of violence are associated with pre-pregnancy obesity, a risk factor for pregnancy complications and adverse maternal and fetal outcomes.

Methods. We studied 1312 women participating in Project Viva. Using the Personal Safety Questionnaire, administered at mid-pregnancy, we assessed experiences of physical and sexual violence in childhood, adolescence, and adulthood prior to pregnancy. We defined obesity as a body mass index ≥ 30 kg/m². Using multivariable logistic regression, we examined associations of violence exposure, timing (childhood/adolescence vs. adulthood), and severity (moderate or severe vs. none) with pre-pregnancy obesity.

Results. In our sample, 185 women (14%) were obese at the start of pregnancy and 497 (37.8%) reported lifetime experiences of violence. Of these, 33% experienced moderate to severe violence. In multivariable models, women who reported ever (vs. never) experiencing violence had higher odds of pre-pregnancy obesity (OR: 1.42; 95% CI: 1.02, 1.99). Experiences of violence during childhood or adolescence (OR: 1.43; 95% CI 1.01, 2.01) and adulthood (OR: 1.72; 95% CI: 1.13, 2.63) were associated with higher odds of pre-pregnancy obesity. Women who experienced moderate or severe violence in childhood or adolescence had higher odds of pre-pregnancy obesity (OR: 2.01; 95% CI: 1.20, 3.36) than those who experienced no violence.

Conclusions. Experiences of violence in childhood, adolescence or adulthood, particularly moderate to severe violence before age 18, were associated with pre-pregnancy obesity. These findings highlight a potential long-term impact of early life abuse or its sequelae on the health of women and their children.
Generating a Data Collection Method for Face Transplantation

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The fields of plastic surgery and transplantation have merged together to produce exciting new surgical procedures in the area of reconstruction. Face transplantation, in particular, has offered a new life to people whose tragic disfigurement forced them to hide away from public eye. Due to the novelty of the procedure, relatively few surgeries have been performed. With so few patients to learn from, and many of them widely distributed around the globe, there is no centralized data collection about the medical experiences of past transplant recipients.

Due to the impressive advantages of REDCap, our team decided to utilize the program to generate a complete database of our past and future face transplant patients. REDCap is a free, secure, web-based application designed for easy data capture in research studies. Our database includes patient information describing demographics, pre-operative data, and post-operative data detailing immune reactions and progress in quality of life, occupational therapy, physical therapy, and speech therapy. Pertinent information about the donor is also included, such as age, skin match, substance use, medical conditions, and immunological cross-matches.

The database is designed so that there will be 1-2 team members who will control data entry in the future, increasing efficiency and minimizing input error. The database has minimal text entry, further reducing input error. Input forms are composed primarily of calculated fields, drop-down lists, radio buttons, checkboxes, and slider scales. Repeated measures from both pre- and post-operative data are organized into “encounters,” rather than pre-fixed scheduled events, allowing more accurate descriptions of patient visits. Encounters can be defined as scheduled or unscheduled, and can be further classified into research or clinical encounters.

To test the quality of our database, we met with several members of the multidisciplinary face transplant team. We asked members to test out the database to see if they could easily and accurately input their data. We altered the database to fit the feedback provided to us. Each team member has very different methods of data collection, so tailoring the method of data entry to them should ensure that future use of the database is optimal.

So far, creation of the database has been welcomed by all of our team members. The next step is to begin data entry, which will allow us to make further improvements. Having a strong foundation for data entry will only become more important as face transplants become more common.
Participation in Physical Activity in Patients 1–4 Years Post Total Joint Replacement in the Dominican Republic

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To address both the growing burden of joint disease and the gaps in medical access for developing nations, medical relief programs have launched programs to perform total joint replacement (TJR) on resident populations in developing countries. Operation Walk Boston has been providing TJRs to patients in the Dominican Republic and collecting data on clinical outcomes since 2008. One outcome of TJR of particular interest is physical activity (PA) since it is strongly linked to general health.

Operation Walk participants undergoing total hip or knee replacement completed preoperative baseline surveys consisting of demographic questions, questions regarding expectations of surgery, and measurements of health-related quality of life. Patients returned to Operation Walk’s 2013 follow-up clinic one to four years postoperatively and were asked to fill out the Yale Physical Activity Survey (YPAS), a reliable tool that measures household, exercise, and recreational components of PA in older adults. We determined the amount of aerobic PA our postoperative TJR patients participated in, and compared it with the levels of PA recommended by the CDC and WHO. We also analyzed preoperative determinants of postoperative participation in aerobic PA in bivariate and multivariate analyses.

64 individuals (mean age 61 years, 80% female) who completed preoperative questionnaires also filled out postoperative questionnaires including the YPAS. 43.3% of respondents met CDC/WHO criteria for sufficient participation in aerobic PA. Multivariate analyses identified several factors associated with higher postoperative PA: age and duration of follow-up influenced PA such that patients who were younger than 65 and at least two years postoperative had an adjusted mean activity dimensions summary index (ADSI) 22.9 points higher than patients who were 65 or older and just one year postoperative. Also, patients who lived with friends or family had adjusted mean ADSI 17.2 points higher than patients living alone; patients who had the most optimistic preoperative expectations of outcome had adjusted mean ADSI scores that were 19.8 points higher than those who were less optimistic.

The postoperative Dominican cohort presented here participates in less PA than recommend by the CDC and WHO, despite having a procedure that generally restores functional status. Our findings suggest that physicians should prescribe exercise and general PA routines to TJR patients in the developing world with a particular focus on patients who are older than 65, recently postoperative, less optimistic about their postoperative outcomes and who live alone.
Skin Cancer Incidence in Patients Presenting for Routine Dermatological Care

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In light of the significant public health problem posed by skin cancer in the United States, the purpose of this research is to identify the rate of skin cancer diagnosis during routine visits to the Medical Dermatology clinic at Massachusetts General Hospital, a busy urban multi-provider setting. Previously, we found that approximately 9% of patients referred for urgent dermatological care were diagnosed with biopsy proven skin cancer in our urgent access setting for same week appointments.

Medical records of patients presenting for routine dermatological care at Massachusetts General Hospital between 03/28/2012 and 09/28/2012 were retrospectively reviewed. All patients diagnosed with nonmelanoma skin cancer (NMSC) histopathologically confirmed by skin biopsy were identified. Demographic information was abstracted from identified patients’ medical records. Billing data from patient encounters was used to derive the total number of patients evaluated and biopsies of skin/subcutaneous tissue performed in Medical Dermatology during the study period. NMSC incidence was then determined in our total clinic population. Mean age, gender distribution, and proportion of patients with each tumor subtype were calculated in the NMSC sub-population.

A total of 14,829 unique patients were evaluated for routine dermatological care among 27 providers during the study period. NMSC was definitively diagnosed in a total of 1,251 skin biopsies in 1,038 unique patients (7.0% of the population). 55% of NMSC patients were men and 45% were women, with a mean age of 69.7 +/- 13.0 years. Among NMSC identified, 61.8% were basal cell carcinomas, 36.9% were squamous cell carcinomas; 1.3% were other non-melanoma cutaneous tumors.

The incidence of nonmelanoma skin cancer in routine general dermatologic care is high and comparable with that observed in our urgent referral setting. Furthermore, the rate of skin cancer is even greater if superficial specimens that limited a definitive diagnosis and melanoma are also included. These findings validate the value of care provided by dermatologists and highlight the likely increasing need for their diagnostic skills as the population ages in the United States.
Dentists and Dental Students in China Treating Patients Living with HIV/AIDS: The Influence of Attitude, Knowledge, and Preparedness

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People living with HIV/AIDS (PLWHA) face multiple barriers to receive the dental care they need, including socio-psychological concerns such as fear of HIV transmission and the stigmatization of the disease as well as a general lack of knowledge in the oral manifestations associated with HIV. HIV-related stigma in health care settings in China have been well documented, with a previous study showing only 63% of surveyed dentists willing to treat PLWHA. However, international studies have shown that improved dental education and training in working with HIV populations significantly reduces the negative attitudes towards PLWHA, making this lack of access to care very preventable.

There is currently an estimated 33.3 million PLWHA in the world, and 780,000 in China. With the incidence of HIV estimated to be approximately 2.6 million people worldwide and 48,000 in China yearly and an improving survival rate, the number of PLWHA who will be seeking dental care in the future continues to grow. Dental care plays a fundamental role in the overall health and quality of life for PLWHA, with oral manifestations associated with HIV or HIV treatment occurring in 50-70% of PLWHA.

In order to better prepare current and future dentists in treating PLWHA, we surveyed dentists and dental students in several hospitals and dental schools in Western, Southern, Northern, and Eastern China, including locations with high, medium, and low prevalence of HIV/AIDS. We received a total of 474 responses from dental students and 394 responses from dentists including general dentists and 11 different specialties.

We will analyze the current status of the attitudes, knowledge, and preparedness that the dentists and dental students in China have towards treating PLWHA. We will be using multivariate analysis to determine the effects that these three factors have on the willingness of dental care providers to treat PLWHA. This information can be used to assess the effectiveness of current dental training and what reform and improvements need to be made to better prepare dentists and dental students in treating PLWHA.
Burden of Disease and the Priorities Guiding US Medical Education Reforms

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Since the publication of the Flexner Report in 1910, medical educators have continued to critique medical curricula and to recommend reforms. While medical education reformers have universally articulated some kind of social vision for medical education, the social visions of medical educators have been diverse. This historical project aimed to identify priorities that have guided US medical education reforms in the past century, especially in terms of social responsibility. More specifically, this project asked to what extent, if any, reformers have endeavored to explicitly match undergraduate curricula content with the prevailing burden of disease – whether in terms of prevalence, morbidity, mortality, or some other measure – of a community.

To address this question, 32 US medical education reports, published between 1910 and 2010, were analyzed. These reports were identified based on existing content analyses published by scholars of medical education and by searches of US medical education organizations including the Association of American Medical Colleges, The Josiah Macy Jr. Foundation, and the American Medical Association. Additional literature searches were conducted in PubMed to identify reports on curricular developments related to the burden of disease.

While certain concerns and priorities have remained remarkably consistent in medical education reform efforts – such as the expansion of biomedical knowledge and the need to reward excellence in teaching – the social concerns of medical education reforms have varied considerably. For example, some reformers have seen the primarily social responsibility of medical education in terms of ensuring an adequate workforce, whereas others have focused almost exclusively on the personal values of students. While some reformers have argued for curricula more tailored to the burden of disease, no systematic effort in the US to match curricula with quantitative measures of the burden of disease was identified.

In contrast, in Ontario, Canada in the 1980s and 1990s, two universities and one multi-university collaboration drew on quantitative population health data to guide curricular priorities: The University of Ottawa, McMaster University, and the Educating Future Physicians for Ontario project. Leaders of these projects frequently expressed their aims in terms of social responsibility.

A major limitation of this project was that content analyzed from US sources was exclusively in the form of published reports, which could not provided a complete picture of medical educators’ priorities.

The next phase of this project will analyze ethical arguments for and against structuring curricula around the burden of disease and offer a normative viewpoint on such aims.
Sharing Trainee Notes With Patients: Understanding the Anticipated Effect of OpenNotes on Resident and Fellow Education and Experience

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OpenNotes is a national initiative allowing doctors to invite their patients to read signed visit notes, through a secure patient portal. Although HIPAA gives patients legal access to their medical records, the process can be prolonged and costly, limiting its utilization. Patients and faculty-level PCPs report positive experiences with OpenNotes, but little is known about its potential impact on trainee education and practice.

We sought to identify trainee and preceptor attitudes about OpenNotes, using a qualitative study of 3 focus groups to inform programmatic and educational strategies. A focus group guide addressed concerns, benefits, and educational implications. Each session was recorded and professionally transcribed. We analyzed transcripts for themes using Crabtree and Miller principles.

Specific concerns included 1) Time burden, with residents feeling vulnerable and downstream of all patient care, and preceptors struggling with time pressure, 2) System mechanisms for editing notes, responding to questions/calls, fixing errors, and educating patients; 3) Disparities for ESL and non-computer literate patients; 4) Sensitive topics like mental health, cancer, substance abuse, rape, obesity; 5) How much to share in notes and uncertainty about what would offend patients, and 6) Who is the note for. Subspecialist trainees and preceptors raised concerns about sharing notes without longitudinal patient relationships. Despite these fears, trainees and preceptors felt that if faculty were sharing notes, trainees should too.

Participants identified several potential benefits, including spearheading innovation, visibility of physician thought process and time spent, improved patient engagement and safety, increased preceptor feedback/supervision, and patient feedback as a possible educational tool. They thought sharing notes might stem use of pejorative language and improve note quality. Some preceptors highlighted more open discussion with patients, including sensitive topics. Trainees and preceptors believed educational interventions should focus on medical students. Trainees in particular emphasized patient (rather than trainee) education and expectation-setting. Both groups provided several specific implementation suggestions.

Trainees and preceptors agree that trainees should be included in OpenNotes, despite concerns about potential effects on the doctor-patient relationship, preceptor oversight requirements, and the sweeping issue of workload and burnout. Transparency with patients may expose existing imperfections in healthcare delivery and “force” improvements leading to better medicine and making physician thought processes “visible” to patients.

As with most focus groups, we are limited by the number of participants. Response bias may result from voluntary participation across specialties, or based on preexisting concerns about or interest in the OpenNotes project.
Hypomyelination in the CNS due to lack of galectin-3 following a prenatal inflammatory insult

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Periventricular Leukomalacia (PVL) is the most common cause of brain injury in preterm infants, characterized by hypomyelination of the cerebral white matter. Activated microglia contribute to the hypomyelination, as they can dynamically shift from neuroprotective to neurotoxic phenotypic states depending on the physiological conditions encountered at the site of injury or infection. Indeed, preliminary results from our rat PVL model demonstrate a marked transient increase in total microglial load with regional variation in cerebral white matter coincident with a persistent hypomyelinated phenotype. Galectin-3, a neuroprotective β-galactosidase-binding lectin expressed on the surface of activated microglia, can downregulate the degree of neurotoxicity and inflammation associated with profuse microglial activation, while promoting pre-myelinating oligodendrocyte (preOLs) differentiation, myelin integrity and function. It is not known whether microglial expression of this neuroprotective galectin-3 is spatio-temporally regulated. We hypothesize that after prenatal inflammatory injury, galectin-3 is not upregulated sufficiently in microglia at the time and site of injury, leading to the inability of pre-OLs to differentiate into myelin-producing mature OLs.

To begin assessing whether prenatal brain insults in the form of hypoxia-ischemia and lipopolysaccharide (LPS) hinder spatio-temporal upregulation of galectin-3 on activated microglia, I characterized the regional variation of total microglial load in areas of interest in the developing cerebrum. Among these areas were the CA1 of the hippocampus, the fimbria, and corpus callosum. On embryonic day 18 rat pups were exposed to hypoxia-ischemia plus lipopolysaccharide (HI+LPS). I collected and processed coronal brain slices containing these regions from 5-6 Sprague Dawley pups (sham control and HI+LPS) at postnatal day 2. After being immunolabeled for microglia (Iba1), total microglial load was assessed using a computerized stereology system (Stereologer). Total microglial load in every region was calculated by multiplying the Iba1 area fraction by the section thickness.

Preliminary results demonstrate a significantly increased microglial load in all areas of interest in the HI+LPS group compared to control (I will enter actual percentage comparisons). Additionally, the microglia of the HI+L group were rounder, suggesting a pro-inflammatory activated state. Lastly, white matter within each of these areas seemed disorganized with diffuse cysts.

Moving forward we will characterize the specific ratio of activated to non-activated microglia within these regions. Paralleling a failure of galectin-3 to upregulate following the inflammatory insult with this increased activated microglial load and with decreased expression of markers of oligodendrocyte differentiation will suggest that activated microglia contribute to the cerebral white matter injury in part by failing to upregulate galectin-3, a promoter of oligodendrocyte differentiation and commitment.
Determining the accuracy of clinical diagnosis of oral lesions and independent risk factors for misdiagnosis.

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The accuracy of clinical diagnosis of oral lesions has a profound impact on the early detection of oral cancer, which is responsible for close to 8,000 deaths annually in the United States, and 120,000 deaths world-wide. Oral lesions are routinely biopsied to ensure that the patient is negative for malignancy, or to detect it at an early stage. This process is initiated by the clinical acumen and suspicion of the surgeon. The goal of this research project is to determine the accuracy of clinical diagnosis of oral lesions by oral and maxillofacial surgeons in order to assess the rate of discrepancy with final histology. Additionally, we look to identify independent risk factors that lead to the misdiagnosis of dysplastic and malignant oral lesions.

We compared the pre-operative clinical diagnosis and post-operative histological diagnosis of oral lesions. The discrepancy rates will be assessed based on lesion type, location, and benign versus malignant designation. Additionally, we seek to identify factors (e.g., age, sex, medical history) that are associated with inaccurate clinical diagnoses. We hoped to reach the goals of the project by pursuing the following specific aims: (1) determine the rate of discrepancy between pre-operative clinical diagnosis and post-operative histological diagnosis of oral lesions; (2) identify factors affecting the discrepancy between clinical and histological diagnoses.

We collected complete information from 1,005 qualifying patients that were seen between 2005-2013. Both the pre-operative diagnosis and histological diagnosis were reclassified into either a worrisome or non-worrisome category. This enables analysis to be clearly presented with the number of missed worrisome cases, which is clinically relevant. Once the clinical accuracies and discrepancies are identified, we will use linear regression and multivariable analysis to measure which patient factors significantly affected the diagnosis. This will hopefully elucidate the reasons for discrepancy, signify individual risk factors, and improve future clinical diagnosis capabilities and prevention.

A limitation of this study was that this project was completed at a tertiary care hospital that is used to a higher volume of pathological cases. Therefore the external validity of these results may only be valid for other hospital based or academic settings with very experienced surgeons. Lastly, it may be possible that the lesions that had an unequivocal pre-operative diagnosis were those most amenable to a more accurate clinical diagnosis. Ultimately, we feel this subset of patients is a balanced representation of the most common oral lesions seen by oral and maxillofacial surgeons.
The Role of p27 in PRKACA-Mediated Resistance to anti-HER2 Therapy

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HER2 is a receptor tyrosine kinase that is overexpressed in 20-30% of all breast cancers, leading to constitutive activation of the downstream RAS/MAPK and PI3K/AKT pathways involved in cell proliferation and survival. HER2 overexpression is correlated with poor prognosis; however, drugs that perturb HER2 signaling, such as trastuzumab and lapatinib, have led to improved outcomes in patients with HER2-positive breast cancer. Unfortunately, many tumors eventually develop resistance to anti-HER2 therapies. Investigation of the mechanisms through which resistance arises may help identify novel therapeutic targets and perhaps ultimately provide better clinical outcomes for patients with HER2-positive breast cancers. Our recent work has shown that overexpression of the alpha catalytic subunit of cAMP-activated protein kinase A (PRKACA) in vitro confers resistance to anti-HER2 therapy and that the kinase activity of PRKACA is necessary for this resistance. Furthermore, immunohistochemical staining of breast cancer samples before and after the development of clinical resistance to trastuzumab-based therapy demonstrated highly elevated expression of PRKACA after the development of resistance, suggesting that PRKACA may play a functional role in resistance in human breast cancers.

To determine the molecular mechanisms by which PRKACA confers resistance, phospho-protein profiling in the setting of PRKACA overexpression and lapatinib treatment was performed. This work identified p27 as a protein that was highly phosphorylated in the presence of PRKACA overexpression. P27, also known as CDKN1B, is a cyclin-dependent kinase inhibitor found in the nucleus that controls cell cycle progression at G1. Phosphorylation of p27 at T198 has been reported to result in trapping of p27 in the cytoplasm and loss of its tumor suppressor activity. Cytoplasmic aggregation of p27 has also been reported in up to 40% of breast cancers. We therefore aim to explore whether PRKACA-mediated p27 phosphorylation is important for the resistance to anti-HER2 therapy observed in the setting of PRKACA overexpression. We first hypothesize that knockdown of p27 will confer resistance to anti-HER2 therapy, and we are testing this using shRNA-mediated suppression of p27. Next, we predict that overexpression of a p27 mutant (T198A) that cannot be phosphorylated will partially or fully abolish the resistance phenotype conferred by PRKACA overexpression. We have generated this mutant construct and plan to test it in our HER2-amplified cell lines in the setting of PRKACA overexpression and lapatinib treatment. Finally, we will perform nuclear/cytoplasmic fractionation on cells overexpressing wild-type PRKACA to determine whether there is localization of p27 to the cytoplasm, as compared to cells overexpressing a kinase-dead version of PRKACA, which fails to confer resistance to anti-HER2 therapy.
Understanding a patient’s goals and preferences for medical treatment during the perioperative period for high-risk emergency surgery: the surgeon’s perspective

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In the practice of modern medicine, shared decision-making is the preferred approach for preference-sensitive medical decisions where the risks and benefits of treatment depend on a patient’s goals and values around medical interventions. In the case of patients with serious illness, who also face decisions about high-risk emergency surgery, understanding the patient’s goals for medical treatment and treatment preferences is crucial to treating patients who may require prolonged hospitalization, or life-sustaining therapy for recovery from surgery or surgical complications. Currently, surgeons do not have a validated, structured approach to elicit patients’ goals and values for medical treatment in the perioperative period.

Understanding surgeons’ views is the first step toward creating a structured approach for surgeons to elicit patients’ goals and values for medical treatment in the perioperative period. To this end, we aim to identify barriers to preoperative conversations about patients’ goals for medical treatment and treatment preferences from the surgeons’ perspective. We will describe surgeons’ attitudes toward preoperative conversations about patient goals for medical treatment and treatment preferences, and assess what types of information surgeons would want to guide decision-making in the perioperative period.

In collaboration with a survey methodologist with expertise in qualitative research, Dr. Cooper and I have designed an interview guide of open-ended and closed-ended questions. We will elicit surgeons’ practices around discussing patients’ goals and values for medical treatment before emergency surgery, understand how surgeons make decisions about whether or not to proceed with surgery, and describe their attitudes toward palliative care. We plan to interview between 15 and 30 surgeons who routinely perform emergency surgeries in patients with serious illness. I will conduct the interviews, and Dr. Cooper will coach me to elicit full responses. Each interview will be transcribed by a medical transcriptionist and analyzed using well-validated qualitative software.

There are a few potential limitations to our approach. Firstly, scheduling to meet with surgeons may be difficult. We will work flexibly to find times that work for surgeons and ensure that the interview is no more than one hour. We also think that surgeons might respond to questions according to a preconceived notion about how they should converse with patients rather than recount the actual conversations that they have with patients. We have designed our data collection tool so as to mitigate the impact of these limitations.
Hippocampal Subfield Volume in Patients Across the Psychotic Spectrum

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Hippocampal volumetric alteration is a hallmark feature of schizophrenia, its significance undetermined. Recent models suggest hippocampal subfields may play significant roles in psychosis pathogenesis. Reduction in glutamate signaling in DG may produce diminished DG-mediated pattern separation and lowered CA3 LTP threshold, resulting in heightened neuronal excitability and increased cerebral perfusion in CA3. Imbalance between (diminished) pattern separation and (enhanced) CA3 pattern completion would foster increased spurious, incorrect associations of memories, manifesting as psychosis.

Though hippocampal volume alteration has been observed primarily in SZ, based on the aforementioned model, we hypothesized: (1) Patients across the psychotic spectrum would demonstrate volumetric alterations in hippocampus and subfields; alterations would be most pervasive in SZ patients. (2) Psychosis subjects would demonstrate volume alterations in CA3 and DG; these alterations would be associated with positive symptoms and susceptibility gene polymorphisms differentially regulated in these areas during the postnatal period.

To test these hypotheses, 419 clinically stable B-SNIP probands, with SZ (n=167), SZA (n=105), or PBP (n=147), completed PANSS and provided DNA samples. T1-weighted MPRAGE scans were obtained for probands and 246 healthy controls. Automated hippocampal subfield segmentation was performed using FreeSurfer to extract: CA1, CA2.3, CA4.DG, presubiculum, subiculum, hippocampal fissure, and fimbria. Hierarchical analyses were conducted to assess volumetric differences in hippocampus/subfields between probands and controls and psychotic groups and controls. Correlations, corrected for multiple comparisons, were conducted to assess associations between subfield volume and positive symptoms.

Results demonstrated bilateral hippocampal volume reduction in probands, compared to controls. Bilateral reductions were observed in CA2.3, CA4.DG, presubiculum and subiculum, and right CA1. SZ revealed reductions bilaterally in CA2.3, CA4.DG, presubiculum, subiculum, and left CA1. SZA displayed reductions bilaterally in presubiculum, right CA2.3 and CA4.DG. PBP demonstrated reductions in left presubiculum, right CA2.3 and CA4.DG.

Analyses of positive symptoms scales demonstrated associations in probands between left subiculum and presubiculum and PANSS positive subscale, left presubiculum and hallucination item scale, and right subiculum and delusional item scale. Analyses of genetic material are ongoing.

Our findings confirm the salience of hippocampal volume reduction in SZ, SZA and BP. Findings in CA2.3, CA4.DG, and presubiculum traverse diagnostic boundaries, distinguishing the latter as significant targets of study in psychosis; alterations in CA1 and subiculum were relegated to SZ. However, associations between positive symptoms and subiculum and presubiculum volumes likely endorse a more complex model of pathogenesis, incorporating multiple nodes of an associative memory network, with potential nuanced differences between psychotic disorders.
What does hydraulic fracturing mean for health and healthcare? Developing a curriculum for healthcare providers in the Marcellus region of Pennsylvania

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Technological advances including horizontal drilling and hydraulic fracturing, commonly known as “fracking,” have made extraction of natural gas from large shale deposits technically and economically feasible. The use of these technologies for unconventional natural gas development (UNGD) has increased over the past decade in many regions of the United States, including Appalachia’s Marcellus Shale. As UNGD moves into communities, concerns about adverse health impacts have grown. Individuals living in communities where UNGD is occurring have sought out their healthcare providers to learn whether symptoms they are experiencing may be linked to UNGD. However, providers may not have adequate information to evaluate and attend to these concerns.

To assess this information gap, we are investigating what community members and healthcare providers in North-Central and Northeastern Pennsylvania, regions of widespread UNGD, already know and would like to know about the potential health risks of UNGD. We will use the results of this assessment to develop educational materials and a curriculum that will supply providers with information about concerns that they and their patients may have and for which there is already a foundation of research.

Our educational needs assessment will consist of focus groups and surveys that will be administered to providers in the Guthrie and Geisinger Health Systems, which have a presence in Pennsylvania counties where UNGD is taking place. Five focus groups of 5-8 participants each will be conducted in October 2013. Two of the focus groups will consist of trauma physicians, two will consist of primary care physicians, and one will consist of occupational medicine specialists. Following the focus groups, surveys will be distributed to a larger sample of Guthrie and Geisinger providers, including physicians, nurses, and nurse practitioners.

Focus group and survey data will be analyzed to identify gaps in knowledge and areas of concern. This information will direct a literature review and expert consultation to inform development of outreach materials, which may consist of pamphlets, posters, Powerpoint presentations, case studies, Podcasts, and/or videos. These materials will be made available at no cost on the Harvard School of Public Health Center for Health and the Global Environment website. The materials will also be presented at a dinner program, conference, or future grand rounds at Guthrie’s Robert Packer Hospital in February, 2014.
Knowledge and Attitudes of Dental Students about Medical Screening by Dentists as Oral Physicians

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There is a growing need for greater access to both oral and primary care at lower cost. Dental care must evolve with the changing health needs of the population. Reductions in health care costs may result when dentists, and more specifically, dental specialists, begin to provide preventive primary care in the dental office. Chairside screening within the dental office can alert a patient to previously undiagnosed or mismanaged disease and subsequent referral to the appropriate doctor by the oral care provider can decrease the prevalence of undiagnosed disease. The introduction of models using mid-level oral care providers, such as Dental Health Aide Therapists in Alaska, raises the concern that a new source of competition may present itself to dentists in the near future.

The population’s need for improved access to care and the possibility of a changing dental care model introduce both altruistic and personal incentives for dentists to transition their role and provide preventive primary care in their practices. There is, however, strong opposition to both expanding the responsibilities of dentists to include limited preventive primary care and the related need to use more mid-level providers such as dental therapists.

This study aims to survey dental students, the next generation of dentists, to determine their current perception of this transition and willingness to provide these services. A survey was developed and pretested to ensure inclusion of the following major areas of concern: contributing factors for choosing the field of dentistry over medicine, attitude towards dentists providing these services, reasons students would/would not consider additional training, extent of training students would be willing to undergo, students’ sentiment toward changing the title of “dentist,” and what the term “dentist” should be changed to for professionals who would provide these services. Preliminary pretest data (n=73) suggests that while the majority of students are willing to provide preventive primary care (83% of respondents) and undergo the training to do so (82%), the feeling towards changing the title of the profession is split, and of the alternate titles, “oral physician” was most popular. Further, with each year of dental school experience, the willingness to provide care, train, and change the name decreased. This preliminary data provides the basis for revising the survey and for distribution to dental students across the US and Canada.
Forming a Pediatric Malnutrition Learning Collaborative in Guatemala: NGO Collaboration

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Guatemala faces the highest rates of childhood chronic malnutrition (stunting) in the western hemisphere and the fourth highest in the world with 49.8 percent of children under five years of age chronically undernourished. Progress in decreasing childhood malnutrition has been slow. While Guatemala has over 10,000 non-governmental organizations (NGOs), limited collaboration occurs between NGOs, and efforts to address malnutrition have been uncoordinated and limited in impact. A learning collaborative (LC) seeks to bring together stakeholders from different organizations to identify problems, learn about best practices, set goals, and create plans to implement change and overcome obstacles.

This study aimed to use qualitative methods to identify best practices and barriers faced by NGOs in efforts to tackle malnutrition and to explore how NGOs can collaborate as part of the development of a pediatric malnutrition learning collaborative involving community health workers and local healthcare providers from different sites in Guatemala.

Twenty open-ended, semi-structured interviews and two focus group discussions were conducted in Spanish during June and July 2013 with community health workers, nutrition educators, coordinators, and directors from three Guatemalan NGOs: Wuqu’ Kawoq, San Lucas Health Mission, and Equipo Técnico de Educación en Salud Comunitaria (ETESC). The interviews and focus group discussions explored barriers to addressing malnutrition, strategies to overcome barriers, as well as best practices and strengths. On July 26, 2013, a conference was held in Xela, Guatemala with twenty-nine attendees representing four NGOs that are addressing childhood malnutrition in Guatemala: Wuqu’ Kawoq, San Lucas Health Mission, ETESC, and Primeros Pasos.

Detailed thematic analysis of the interviews and focus group discussions will occur in the upcoming months. Barriers to addressing malnutrition include limited resources, corruption, short-term projects, inadequate water supply, lack of continuous employment, environmental factors, machismo, and limited family planning. Successful strategies include directly observed nutritional supplementation and deworming, more frequent follow up with families, interactive nutritional education, and community engagement. Anonymous feedback from conference attendees suggests the conference and idea of forming a pediatric malnutrition learning collaborative were well received, and attendees expressed interest in additional meetings and further exchange of ideas. Attendees also proposed site visits between NGOs and forming working groups to focus on different aspects of malnutrition. Directors from each of the organizations will have a conference call in the near future to discuss how to move forward and possibly plan a joint effort or focus area between NGOs.
Patient Comprehension of Emergency Department Discharge Instructions: 
A Pilot Study

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Health literacy is defined by the NIH as “the degree to which individuals have the capacity to obtain, process and understand basic health information needed to make appropriate health decisions and services needed to prevent or treat illness.” Limited health literacy is recognized as a major determinant of health outcomes, affecting half of American Adults and costing $73 billion annually. Despite increasing attention, health literacy is still an unknown entity to many providers, and even less is known about its impact in the ED. In this study, we will determine the baseline health literacy rate of patients attending the Beth Israel Deaconess Medical Center (BIDMC) Emergency Department (ED) in Boston, MA.

We performed a prospective, observational, pilot study of a convenience sample of adults who presented to the BIDMC ED. Participants were screened with The Short Test of Functional Health Literacy in Adults (S-TOFHLA), an established health literacy screening tool. We also administered a survey of patient understanding of health care interactions and treatment as well as patient opinion of health provider-patient communication.

Of the 75 people surveyed, the majority was under the age of 45 (51%), female (65%), White (53%), with Private health insurance (67%) and whose primary language is English (91%). Most had completed college and post-college education (45%), were currently employed (61%), and had personal doctors (88%). The majority felt their level of reading was excellent (85%) and never needed assistance when reading materials from their doctor or pharmacy (85%) and were confident in filling out medical forms by themselves (75%). Regarding satisfaction data, most patients felt their doctor and nurse explained their problem excellently (52% and 71%, respectively) and felt the overall communication from the doctor and nurse was excellent (57% and 69%, respectively).

The results show that our study population is generally satisfied with the health care team’s care and communication. Patient perception data needs to be stratified against the demographic data to determine areas where understanding is lacking and where dissatisfaction exists. We can then learn where to target our improvement efforts for those who are explicitly dissatisfied with their visit and communication. However, further data analysis needs to be completed to determine whether the cohort overall, regardless of their perception, objectively understood their diagnosis and treatment plan. The data will then show how well a patient’s perception of their health literacy is aligned with their actual understanding.
Understanding the experience of schistosomiasis illness among vulnerable Zambian preschoolers: Healthy Learners Program

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Schistosomiasis is an infectious disease which disproportionately affects poor and vulnerable children in developing nations and is associated with significant acute and chronic morbidity. The infection is easily diagnosed (by urinalysis) and treated (with praziquantel). This quality-improvement study sought to understand infected children's complete experience of illness, from assessment of risk factors for infection to emotional reaction to diagnosis and treatment and follow-up care received.

Communities Without Borders (CWB) supports approximately 1500 orphans and otherwise vulnerable children (OVC's) in the peri-urban slum compounds of Lusaka, Zambia. In 2012, the CWB Healthy Learners Program (HLP introduced school-based health screenings and preventative care to six CWB-supported community schools; screenings included urinalysis and praziquantel treatment for schistosomiasis. This current project targeted students who were diagnosed and treated for schistosomiasis in 2012.

Students’ most common emotional responses to diagnosis (2012) were sad (29%), ambivalent (21%), scared (13%), and happy (13%). Upon receiving praziquantel, a majority of respondents felt happy (63%) with other major emotions ambivalent (13%) and sad (8%). In addition, 46% of children reported having one or more other household members with a diagnosis history of schistosomiasis. While some students reported playing or taking baths outside (21%), the majority report that they do not (75%). None of the students reported any contact from a public health nurse or other follow-up care after their 2012 diagnosis.

Although responses to diagnosis and receipt of treatment were mixed, a majority of students felt happy (63%) upon receiving praziquantel. Given the ease and acceptability of diagnosis and the low cost of treatment, a school-based approach to schistosomiasis may successfully improve children's medical health and quality of life. Our surveys also revealed a high prevalence of other infected household members, suggesting that the diagnosis in one child should also prompt testing and treatment of other household members.

Rivers and dams are potential infection sites, and differing water sources may explain infection disparities across communities. Finally, appropriate follow up is not occurring in the current model. Strengthened partnerships with local health centers and the Lusaka District Ministry of Health office should be sought and health promotion education programs in schools and communities should be developed.

Limitations of this study included high rates of student turn-over and school absences, as only 24 of 51 students identified in 2012 with schistosomiasis were surveyed. Linguistic and cultural barriers were minimized by use of Zambian medical students as interpreters and cultural brokers.
Sterile Vitritis in the Setting of a Boston Keratoprosthesis

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Purpose: To revisit the clinical paradigm attributed to Boston Keratoprosthesis (KPro) patients presenting with idiopathic culture-negative vitreous inflammation.

Methods: A retrospective chart review was performed of 346 adult patients with a keratoprosthesis, performed by three surgeons (JC, KC, CHD) at Massachusetts Eye and Ear Infirmary from January 2000 to August 2013.

Results: 38 patients developed vitreous inflammation between 2 days and 8.5 years postoperatively. 23 cases (43 total episodes) showed no obvious cause for inflammation. The proportion of patients who fit the paradigm of idiopathic, culture-negative vitreous inflammation (“sterile vitritis”) is small (8/23). 7/23 patients presented with signs and symptoms similar to infectious endophthalmitis but were culture-negative. Vision decline was variable (median loss of 9 lines on Snellen Chart, range 0-24). Median time to best vision was 8.9 weeks (range 0.86-36.7). 10/43 episodes did not recover to baseline vision. 12/23 patients had repeat bouts of vitritis. 17/23 later developed retroprosthetic membranes (13), glaucoma (8), cystoid macular edema (3), and retinal detachment (2).

Conclusions: Many cases of vitreous inflammation after KPro have no identifiable trigger. The paradigm for sterile vitritis after KPro implantation includes sudden, painless loss of vision with full recovery of vision upon treatment with periocular steroids. However, this does not apply to all cases. Sterile vitritis can mimic infectious endophthalmitis, yet be culture negative. Vision may not increase back to baseline. Sterile vitritis may be a part of a common pathway of chronic inflammation after KPro.
Evaluating Promotion and Implementation of the National Prevention Strategy

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In 2010, the National Prevention, Health Promotion and Public Health Council was created, comprised of the heads of 20 federal agencies and chaired by the Surgeon General. The Council published a comprehensive National Prevention Strategy in 2011, highlighting four Strategic Directions and seven Priorities for furthering prevention in the United States. A second body, the Advisory Group on Prevention, Health Promotion, and Integrative and Public Health was created at the same time as the Council and consists of 22 non-federal prevention experts. The Advisory Group exists to provide recommendations to the Council on how to best achieve the Strategy’s goal of increasing “the number of Americans who are healthy at every stage of life.”

It is very difficult to capture how effective the National Prevention Strategy has been. The Office of the Surgeon General’s view is largely confined to the actions of the federal government, even though this only represents a small part of the Strategy’s framework. During my summer in the Office of the Surgeon General, we saw an opportunity to engage with the diverse members of the Advisory Group as a resource to provide context about the Strategy in action around the nation.

Given the dearth of information about implementation and promotion of the Strategy and the necessarily subjective view of the Advisory Group, we decided to pursue a qualitative evaluation project using scripted phone interviews. We hoped to accomplish three specific aims with this project: to collect information on the promotion and dissemination of the Strategy, information on their experiences in implementing the Strategy, and specific examples of the Strategy in action.

During my time in the Office, I conducted 11 interviews ranging from 30-60 minutes in length. This allowed me to pull out overarching themes including (but not limited to) the need for broader dissemination of the Strategy, the Strategy’s relationship with the Affordable Care Act, the need for new and creative types of partners, the role of the Surgeon General, and the need for concise and actionable supporting resources. We soon realized that given the small sample size and the subjective view of the Advisory Group members, much work remains to be done to gauge the effectiveness of the Strategy around the nation. Nevertheless, this project provided a number of helpful recommendations for the Office and left behind an analysis framework that can be adapted to further evaluation efforts.
Development and pilot-testing of a vitiligo screening tool

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Vitiligo is a common acquired disorder of depigmentation characterized by involvement of skin, hair and/or mucous membranes. It affects 0.1-8.0% of the population in various regions of the world, with an estimated prevalence of ~1% in Europe and the United States. Vitiligo affects men and women equally and can present at any age. The pathology of vitiligo is complex and not yet well understood, influenced by multiple genes and environmental factors.

Studies aimed at understanding the genetics, pathology, and therapeutic response of vitiligo rely on asking a single question on a survey about ‘physician-diagnosed’ vitiligo to identify study participants for research. However, this type of self-reporting is not sufficient to validate a diagnosis of vitiligo and thus limits the ability to accurately study the condition. To address this, we developed and pilot-tested the VItiligo Screening TOol (VISTO) as a means to confirm vitiligo diagnosis and determine phenotype in an outpatient clinic population. The objective of this study was to determine if the VISTO is a sensitive and specific instrument for the detection of vitiligo in an adult population.

The VISTO is a self-administered questionnaire that consists of 8 closed-ended questions. It assess whether the respondent has ever been diagnosed with vitiligo by a healthcare provider and uses characteristic pictures and descriptions to inquire about the subtype and extent of disease. 147 patients with or without a diagnosis of vitiligo were recruited to complete the questionnaire at the Brigham and Women’s Hospital outpatient dermatology clinic. A board-certified dermatologist confirmed or excluded the diagnosis of vitiligo in each subject. 140 completed questionnaires were included for analysis, 43 cases and 97 controls. The pictorial question had 100% sensitivity and 99% specificity for the diagnosis of vitiligo. Answering “yes” to being diagnosed with vitiligo by a dermatologist and choosing one photographic representation of vitiligo had 95.2% sensitivity and 100% specificity for diagnosis of vitiligo. Based on these results, the VISTO is the first validated questionnaire that is highly sensitive and specific in identifying vitiligo among adult English speakers. Study limitations include lack of significant number of patients with other disorders of hypopigmentation and that the study was conducted in a hospital-based dermatology clinic with patients who have access to a dermatologist. Further study is needed to determine generalizability. We believe that the VISTO can be used to improve large scale epidemiologic and genetic studies in an efficient and cost-effective way.
Characterizing Dystrophin as a Prognostic Biomarker in Surgically-resected GIST

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Dystrophin (DMD) is a 2.2Mb, 79-exon gene classically attributed to various forms of muscular dystrophies, including Duchenne’s muscular dystrophy. Recent evidence has also shown highly localized, large-intragenic deletions in DMD, as well as down-regulation of the dystrophin protein, in metastatic myogenic cancers, thereby suggesting its role as a tumor suppressor.

Gastrointestinal Stromal Tumors (GIST) is the most common type of myogenic cancers caused by activating mutations in KIT or PDGFRα tyrosine kinases. Patients with localized GIST lesions have often been treated surgically, followed by adjuvant imatinib therapy (Gleevec) in those classified as high-risk. Because no molecular biomarkers are used to biologically predict tumor recurrence and metastasis, many patients falsely classified as high-risk (via tumor size, location, and mitotic count) must adhere to an expensive regimen with the risk of side effects.

In this study, we hypothesized that DMD may serve as a prognostic molecular biomarker to stratify risk of tumor recurrence and direct adjuvant therapy only to patients with high metastatic risk. Since large-intragenic deletions have only been identified in DMD, alternative genomic mechanisms that result in intact but dysfunctional dystrophin may still exist.

To identify such mechanisms, we utilized both Sanger and next-generation sequencing. First, five DMD coding regions (exons 21, 37, 48, 53, and 59) containing a high frequency of single nucleotide variants (SNVs), some of which may lead to loss of dystrophin function, were identified in the Leiden Muscular Dystrophy database. Such mutations might also have pathological roles in myogenic cancers and were therefore screened for in twenty-six cases of primary and metastatic myogenic cancers via Sanger sequencing. The Affymetrix Haloplex Illumina exome-capturing platform was simultaneously used to analyze the entire DMD gene and other candidate genes in the dystrophin-associated glycoprotein complex.

Sanger sequencing results have identified benign SNVs previously reported in the Leiden Muscular Dystrophy database. An E2910V, N2912D double variant was also identified in one metastatic Leiomyosarcoma (LMS) lesion with intact dystrophin expression. This variant has been previously reported to alter protein folding and melting temperature, suggesting a possible deregulatory function in the protein.

Because only five exons were explored in dystrophin (2.2Mb, 79 exons), additional small-scale mutations that inactivate dystrophin may also be found in coding and non-coding regions. Currently, we have prepared and are currently validating gene libraries for the exome capture process. We hope to identify additional small-scale mutations in different portions of the DMD gene and discover additional tumor suppressor candidates in the dystrophin-associated glycoprotein complex.
A convection-enhanced bioartificial pancreas for the treatment of Type 1 diabetes.

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Immunosolated macroencapsulation (iMED) of pancreatic islets, a subcutaneously implanted bioartificial pancreas, restores glucose homeostasis in mouse models of Type 1 diabetes (T1D). These devices offer low-maintenance and low-risk therapeutic equivalents of protected pancreas transplants, eliminating the need for insulin injections or immunosuppression. Despite their promise, current iMEDs have yet to reach the clinic because they depend on passive diffusion to harvest nutrients from the surrounding host tissue. Because diffusion is limited to ~100 µm within the capsule surface, current iMED designs can only sustain a wafer-thin layer of cells (~216 islets). Given that > 500,000 islets are required to maintain euglycemia in humans, a T1D patient would require more than 125 of these devices, making iMEDs impractical for T1D therapy. Although many biotech companies and laboratories have attempted to design better iMEDs since the 1990s, no iMED geometry has yet been able to overcome the cell-number limitations that prevent clinical efficacy.

A simple, minimally invasive iMED capable of sustaining physiologic numbers of islets could change the standard of care for Type I diabetics. We hypothesize that improving nutrient transport throughout the cell capsule will generate such a clinically relevant device. We have designed and fabricated a convection-enhanced iMED (ceMED) that perfuses cells beyond the ~100 µm diffusion limit. Preliminary testing of the ceMED in vitro has demonstrated that nutrients circulate rapidly through encapsulated cells to the boundaries of a 2.4 mm-thick capsule (0.2 cm³ volume), whereas nutrient diffusion within static control capsules is below the detection threshold after 24 hours. These early results support the hypothesis that a ceMED may overcome the cell-sustaining limitations of iMEDs, which would make ceMEDs a promising alternative to conventional T1D therapies.

We are currently determining how many islets may be sustained within our ceMED prototype. Additionally, we are testing ceMEDs in vitro for glucose-stimulated insulin secretion to verify that the encapsulated cell population responds physiologically to hypoglycemia, euglycemia, and hyperglycemia. We are also implanting prototype ceMEDs in mice to demonstrate if these devices (1) sustain greater populations of encapsulated cells than iMEDs and (2) restore euglycemia in T1D mouse models. We expect these studies to provide a compelling proof-of-concept that ceMEDs offer a clinical solution to T1D.
Subjective and biological response reactivity to a pain challenge in the course of repeated patterns of sleep restriction and recovery – a pilot study

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Patterns of restricting sleep during the week and ‘catching up’ on sleep over the weekends are pervasive in modern society. Many people believe that the human body will habituate to those patterns, but it is currently unknown whether biological stress systems, such as the hypothalamic-pituitary-adrenal (HPA) axis, habituate, or sensitize in the context of recurrent sleep restriction-recovery patterns.

We hypothesized that in the context of repeated sleep restriction and recovery, subjective and biological responses to a stressful challenge sensitize, i.e. show increased reactivity to challenge, without complete response normalization during periods of recovery sleep.

To test this, healthy participants had two 25-day in-hospital stays separated by a minimum of 2 months. In the sleep restriction stay, participants underwent 3 cycles of 5 nights of 4-hour sleep (0300-700h) followed by 2 nights of 8-hour recovery sleep. In the control stay participants had 8 hours of sleep (2300-700h) per night. Participants underwent a stressful pain challenge, i.e. the cold pressor test, on 7 days of the protocol, i.e. on the baseline day, every fifth day of sleep restriction and every second day of sleep recovery at baseline. The cold pressor test requires the immersion of the hand in ice-cold water (3°C), until pain tolerance is reached. During the test, participants had to rate the intensity and unpleasantness of the sensation on visual analog scales every 10 seconds, and nurses took blood at various time points pre- and post-challenge. Cortisol, the main effector hormone of the HPA system, was measured in serum and cortisol reactivity was calculated as increase from pre-to post-pain challenge. Pain tolerance was measured in seconds from hand immersion to hand removal.

During my project period, I entered, organized, and analyzed the main outcome variables cortisol, pain tolerance, pain intensity, and pain unpleasantness from 10 participants in each condition.

Results reveal a significant interaction effect (p<0.05) for pain tolerance, indicating that participants in the sleep restriction condition do not get more tolerant to the pain across days as observed in the sleep condition.

We also observed an increase in subjective pain intensity/unpleasantness ratings over the course of repeated sleep restriction, which do not return to baseline during the sleep recovery periods. These preliminary findings suggest that sensitization occurs in response to sleep restriction, resulting in increased reactivity to a stressful event. Sensitization may constitute a potential mechanism through which common patterns of sleep restriction and recovery affect disease vulnerability.
A Business Case for Oral Physicians: Market Analysis and Potential Practice Models for Dentists to Address the United States Primary Care Shortage

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The United States is experiencing a dramatic shortage of primary care providers that is expected to worsen over the next decade, primarily from population growth and health care reform. The current environment is failing to adequately diagnose the nation’s growing systemic health issues. Estimates predict that there are eighty million people affected by cardiovascular disease and twenty-three million people with diabetes mellitus, one-third of which are unaware of their condition. Early screening for these and other conditions can elucidate risk factors for patients and help to prevent disease through medical intervention and counseling. One possible measure to address the primary care gap is in the dentist’s office. Dentists are already trained in all manner of systemic illnesses, especially those that can manifest in the oral cavity. Both medical and dental communities are increasingly accepting the concept of the oral physician, a dentist who can provide medical screening and limited primary care. In order for dental professionals to widely endorse their necessary role as oral physicians, it is important to develop a sustainable business model that not only addresses oral and systemic health, but also ensures the financial success of the dental practice. This research aims to conduct a market analysis for the oral physician by estimating the population receiving oral health care but not medical care, and has an undiagnosed health condition, estimate the total costs of non-intervention in the form of medical costs, and evaluate fee-for-service, concierge/direct pay, and hybrid practice models in terms of revenue, costs, and efficiency. Estimates of those with undiagnosed health conditions that could be screened by a dentist are notable: Diabetes (784,043), hypertension (432,241), hypercholesterolemia (160,405), obesity (628,285), tobacco use (2,232,839), and alcohol use (2,232,848). The total medical costs of non-intervention for these populations were approximately $15.2 billion per year, as estimated by the most recent economic analysis of those conditions. What remains to be determined is the ideal business model for the oral physician. One approach is the concierge model, which allows the practitioner to maintain a smaller patient pool by collecting annual payments for premium services such as next-day appointments, phone/email contact with the doctor, and discounted fees. Other models may include global payments covered by insurance and integration with Accountable Care Organizations. Further investigation into reimbursements, legislation, and feasibility must be all assessed before the field of dentistry can formally endorse this mode of practice.
Evaluating Health Model implementation in Navajo Nation Chronic Disease Care

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On the Navajo Nation, the Community Outreach and Patient Empowerment (COPE) Project represents a collaboration between Brigham and Women’s Hospital, the Indian Health Service (IHS) and the Navajo Division of Health. COPE utilizes community health representatives (CHR) to reduce chronic disease burden and decrease health disparities; among Navajo patients, diabetes-related mortality rates are 60% higher than white Americans. Managing chronic disease among Navajo patients presents significant cost, human resources, and logistical challenges given high patient-loads and extreme travel distances for patient care. COPE first provides chronic disease education and management training to CHRs who in turn extend this knowledge to patients, and, second, facilitates CHR integration with the IHS care process.

The project sought to assess qualitatively those factors which facilitated and impeded COPE implementation. Factors included 1) facility organization such as staff size, size of catchment area, staff turnover; 2) COPE stakeholder involvement; and 3) integration of CHRs with IHS clinic-based staff through access to electronic health records (EHRs), referral feed-back to providers, and involvement in case management.

We completed ten interviews with COPE leadership, CHR supervisors, and COPE-affiliated IHS providers across five of eight COPE service units, each chosen because of multi-year COPE involvement. Subjects received an anonymous survey with scaled responses indicating level of agreement with prompts, and then proceeded through a structured, unrecorded interview which varied depending on the scope and depth of the subject's responses. Survey responses were scored using a Likert scale, and mean scores as well as percent response rates were calculated. Written qualitative responses were coded by theme.

Interview and survey data show broad IHS and tribal health division support for COPE, though subjects identified areas for improvement. Data also showed a clear, strong need to improve CHR integration with clinic-based staff, as few had EHR access and were thus involved in IHS case management. Participants observed that the IHS electronic health records access policy severely impeded first-phase CHR incorporation; resultantly, CHRs currently do not communicate effectively with providers about patients that are referred to them. Further, interview data show providers are unaware of COPE’s quantitative impact. While COPE has collected data and compared the intervention relative to standard IHS patients internally, interview data show stakeholders remain unaware of COPE’s effect, which in turn seemed to affect perception of the healthcare model.

Limitations include a small sample size; additional stakeholder interviews would improve generalizability of data.
History of Dance Medicine

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Despite the extensive history of dance, beginning with ballet in the 15th century, it is only in the last two decades with the founding of the International Association for Dance Medicine and Science that the medical care of dancers has become an organized and recognized subspecialty. Dance medicine is a multi-disciplinary subspecialty that specializes in the treatment of the musculoskeletal injuries as well as other dance-related health needs, including mental health, of dancer patients. Injuries are common at all levels of training with data reporting that 67-95% of dancers sustain an average of 1.7 to 6.7 injuries in a year, largely due to overuse injuries of the lower extremity. To better understand the field’s trajectory, I examined the unique origins of this subspecialty.

The late 20th century was a period that witnessed a proliferation of medical subspecialties. This allowed sports medicine and performing arts medicine to form. Given the status of dance at the intersection between arts and athletics, I am interested in dance medicine’s relationship to these fields. To this end, I conducted twelve semi-structured interviews with dance medicine pioneers of vastly different backgrounds and geographic locations.

In the early 1970s, dancers and dance educators witnessed the benefits that athletes received from sports medicine, a field led by orthopedic surgeons, and began to seek their medical advice. Individual orthopedic surgeons observed many similarities between dancers and athletes. While some injuries are unique to dancers because of the aesthetic demands of the art form, this alone does not account for how dance medicine became a distinct entity. The key distinction emerged as healthcare providers realized that the dancers self-identified much more as artists than athletes, yet their needs were more similar to athletes than musicians and vocalists, thus could neither group them in sports medicine or performing arts medicine. Dance medicine, unlike any other medical specialty, became a distinct subspecialty driven by patients and not the medical profession.

The oral histories I obtained revealed another important dynamic: though focused on the needs of dancers, dance medicine has yielded insights that are valuable more broadly. In particular, eating disorders and HIV are two diseases that have emerged earlier and in disproportionate prevalence in dancers, bringing them to the attention of the medical community as well as the public.

The interviews revealed that the emergence of dance medicine was a combination of fortuitous events and opportune timing. Individuals who were invested in the well-being of dancers, a small but unique population, were brought together to bring awareness to dancers’ needs and propel the advancement of better care.
The shortage of surgeons, obstetricians and anesthesiologist in low- and middle-income countries

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A lack of surgical providers is a major barrier to essential surgical care worldwide. The surgery workforce deficit is particularly concerning due to epidemiologic trends towards non-communicable diseases, many of which require surgical treatment. Yet the global surgery workforce has not been comprehensively studied. The goal of this research was to establish data regarding the number of surgeons, obstetricians and anesthesiologists world-wide, and to assess the correlation between the density of surgical physician providers and maternal mortality.

We performed a systematic search and literature review of the English-language literature regarding the number of surgeons, obstetricians and anesthesiologists practicing in low- and middle-income countries (LMICs). We also consulted the homepages of World Health Organization (WHO), Organization for Economic Cooperation and Development (OECD), and international and regional professional societies.

Across LMICs, general surgeon density ranged from 0.13 to 1.57 per 100,000 people; obstetrician density ranged from 0.042 to 12.5 per 100,000; and anesthesiologist density ranged from 0 to 4.9 per 100,000. Maternal mortality was reduced by 14% for every increase in surgical physician per 1,000, when controlling for both health expenditure as percent of GDP and percentage of births attended by a skilled health personnel (p=0.018). Surgical densities were collinear with GNI per capita. Literature describing the number of surgeons, obstetricians, and anesthesiologists in LMICs represented only a small minority of LMICs, with data for all three specialties available for only five countries.

Surgical physician density is often 100 times lower in high income countries compared to LMICs. The Global Surgery Workforce Initiative (GSWI) was created to address the surgical workforce shortage. The GSWI is currently surveying 130 Ministries of Health and 200 surgery-related professional organizations to determine the number of surgical physicians and non-physicians in LMICs. GWSI data can provide a detailed understanding of the global surgical workforce and inform surgical systems strengthening efforts on international and national levels.
The Role of Sirtuin 1 in Exercise-Induced Angiogenesis in Skeletal Muscle

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Systemic health benefits of endurance exercise include decreased risk of cardiovascular disease, improved insulin sensitivity, prevention of age-associated sarcopenia and lipodystrophy, and decreased chronic inflammation. It is believed that these health benefits are mediated in part by exercise-induced adaptations of skeletal muscle tissue. The mechanisms whereby alterations in cellular energy state are sensed and how these signals are then transduced into coordinated physiological adaptations in skeletal muscle are subjects of intense investigation.

The mammalian sirtuin family consists of seven evolutionarily-conserved proteins (Sirt1-Sirt7) which regulate whole-body metabolic homeostasis and stress resistance. Of these, Sirt1 is the closest human homolog of Sir2, a protein that regulates longevity in response to caloric restriction in S. cerevisiae, C. elegans, and D. melanogaster. Specifically, Sirt1 is a NAD+-dependent deacetylase that regulates cellular energy output and metabolic homeostasis. Recently, it has been discovered that Sirt1 can deacetylate and activate PPAR-γ coactivator 1α (PGC-1α), a transcriptional coactivator that is strongly upregulated by endurance exercise in skeletal muscle. Furthermore, it has been reported that Sirt1 regulates angiogenic behavior of endothelial cells through downregulating Notch signaling. We hypothesize that Sirt1 in vascular endothelial cells is required for exercise-induced microvascular remodeling of skeletal muscle.

We therefore sought to use endothelial cell-specific knockout animal models of Sirt1 and in vitro studies to clarify the physiologic role of Sirt1 in mediating exercise-induced angiogenesis in skeletal muscle. Using in vitro studies, we demonstrated that siRNA-mediated knockdown of Sirt1 in a mouse endothelial cell line (MS1) impairs cell migration in a wound-healing assay and impairs chemotaxis in response to vascular endothelial growth factor (VEGF) in a Boyden chamber assay. Furthermore, we demonstrated that Sirt1 knockdown impairs migration of MS1 cells toward cultured mouse myofibers (C2C12) overexpressing PGC-1α, an in vitro model of exercise-induced angiogenesis. These observations suggest that Sirt1 may be required for exercise-induced angiogenesis in skeletal muscle tissue in vivo. Currently, endothelial cell-specific Sirt1 activity knockout (Tie2-Sirt1-KO) mice are being produced by mating Sirt1-exon4-flox mice (with LoxP sequences flanking exon 4 of the Sirt1 gene, which encodes the catalytic domain of Sirt1) with Tie2-Cre mice (in which expression of the Cre recombinase is driven by the endothelial cell-specific Tie2 promoter). Tie2-Sirt1-KO and wildtype mice will undergo a regimen of endurance exercise through voluntary wheel running. In skeletal muscle biopsies, exercise-induced angiogenesis will be quantified by imaging FITC perfusion within muscle vasculature and via immunohistochemistry.
Early life factors associated with caries in children at 6.5 years

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Dental caries is one of the most prevalent chronic childhood diseases worldwide, and has the potential to impact childhood eating habits, nutritional intake, and quality of life. Identification of early life risk factors will be essential for identification of high-risk children and development of preventive strategies. Deciduous teeth develop prenatally and during the first year of life, therefore environmental exposures during this time period are particularly relevant in relation to development of the dentition and risk of caries.

In this study, we utilized the large birth cohort of mother-infant pairs from the Promotion of Breastfeeding Intervention Trial (PROBIT) to examine the relationship between dental caries at 6.5 years and early life factors. These factors included birth weight, gestational age, APGAR score at 5 minutes, delivery mode, infant feeding at 12 months, prenatal and environmental tobacco smoke exposure, use of probiotics, and use of inhaled medications. Descriptive statistics and bivariate analyses were conducted for all variables of interest. The outcome variable for multivariable analysis was decayed, missing, or filled teeth (DMFT) at 6.5 years of age, which was modeled as a count variable using negative binomial regression analysis. The hospital/polyclinic site was included as a random effect, and the regression model was adjusted for individual covariates, including socioeconomic factors.

In the fully adjusted multivariable model, children who were born with higher birth weight or gestational age had a higher prevalence of DMFT at 6.5 years, while no associations were found with Apgar score or delivery mode. Among feeding variables at 12 months of age, breastfeeding and increased number of times per day of formula, juice and other liquids were associated with increased DMFT at 6.5 years. No other significant associations were observed between early life factors and DMFT in the multivariable analysis.

While prior literature on the association of early childhood caries with breastfeeding, birth weight, and gestational age has been conflicted, our results confirm prior evidence establishing the relationship between caries and frequency of non-water liquids. While the study may have limitations in generalizability to populations outside Belarus, our results nevertheless provide an important contribution to the literature. As one of the largest studies to examine these associations and as a cohort analysis, our study provides important new arguments on the relationship between caries and perinatal factors. In conclusion, these results are highly suggestive that factors during the first year of life influence the development of early childhood caries.
Analysis and Comparison of Delays to Treatment Initiation and Protocol Deviations in a patient cohort treated for rhabdomyosarcoma in the USA and Guatemala

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Over 150,000 children are diagnosed with cancer each year. For those that live in developed countries, approximately 80% will survive; however children in developing countries have an average survival of just 10%. Through twinning programs with pediatric oncology programs in developed countries, many developing countries have made strides in treating the most common cancers, especially leukemia and lymphomas. Unfortunately the progress has not been as marked in solid tumors.

Rhabdomyosarcoma is a relatively rare soft-tissue tissue that arises from muscle precursor cells. Since the 1970’s a series of four clinical trials raised survival for localized disease to approximately 80% using common chemotherapeutic agents. However, when this protocol is used in developing countries, the survival rates are much lower. In Guatemala, the reported survival rate for localized disease is about 50%. There are a multitude of possible explanations for this disparity, ranging from differences in disease biology and poor quality of pharmaceutical agents to delays in diagnosis and deviations from protocol during treatment.

This study set out to examine the latter two possibilities (delays in diagnosis and treatment initiation, and then delays and deviations during treatment) through a retrospective cohort analysis. Patients treated between 2005 and 2010 in Guatemala at the Unidad Nacional Oncologia Pediat्रica and Boston Children’s Hospital in the USA were analyzed for the time to diagnosis and delays during treatment. Currently only data from the Guatemalan cohort has been recorded, and statistical analysis is on going; analysis of the US patient cohort is beginning.

The survival in the current Guatemalan cohort of 42 patients was actually lower than that reported previously in the literature, event free survival was just 30%. When patients who abandoned treatment were censured from the cohort, survival was still just 39%. We hypothesized that the lower survival would be in part due to lengthy delays in treatment and deviations in dosing; however, there does not appear to be a difference in treatment intensity of chemotherapy or radiotherapy between those Guatemalan patients who survived and those who died. Surgical outcomes were very difficult to analyze, but were consistently poor across groups.

While comparison to the US cohort and statistical analysis is still necessary, it appears that deviations and delays in the initiation and completion of treatment do not account for the differences in survival between the US and Guatemalan patients. Further work is needed to explore other possible explanations such as differences in disease biology.
The Perspectives of Young Women in Siaya County, Kenya: Their Lives and Their Thoughts on Cash Transfer Programs

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Background: Unconditional cash transfer (UCT) programs provide money to eligible individuals, without dictating how these individuals spend the money or tasks that they must do to continue receiving money. Though different UCT programs use different eligibility criteria, many programs use a means test to target UCTs to the poorest people in a given region.

Purpose: To investigate the lived experience and perspectives of women receiving cash transfers; to compare and contrast: (1) How women receiving different cash transfer amounts think about their future goals; (2) How they feel about their well-being (including psychological well-being); and (3) What they think about UCTs.

Methods: Innovations for Poverty Action is a research organization conducting a randomized controlled trial (RCT) to evaluate a UCT program being implemented by a non-profit called GiveDirectly. The program is for women, ages 18 to 19 at baseline, living in extreme poverty in rural Siaya County, Kenya. The RCT includes three study groups: (a) 37 women receiving a $1,000 transfer, (b) 40 women receiving a $500 transfer, and (c) 82 women receiving no transfer. The RCT is evaluating quantitative data on numerous outcomes, including socioeconomic status, goals, and health and psychological status.

Working with an interpreter, I conducted semi-structured, in-depth interviews with 30 women enrolled in the RCT (10 from each study group) for approximately one hour, using an interview guide that addressed each study aim. I audio recorded and transcribed each interview. Using qualitative methods, I will analyze the transcripts to determine important narratives and themes instantiated by interviewee quotes. I will then use Atlas.ti software to label quotes with themes, and examine how themes interrelate.

Results: Though this analysis is not yet complete, initial observations include the following. Across all study groups, social and economic factors were dominant in shaping future goals, e.g., the limited local employment opportunity structure available to interviewees. Across all study groups, interviewees described their general and psychological well-being in terms of meeting basic needs, such as shelter and food, thus ‘re-socializing’ well-being. The UCT program was well-received by interviewees, though the program was temporary. The experience of receiving a UCT was shaped by other aspects of their lives, such as their religion, cultural obligations, respect for family members, and the desire to be treated with respect themselves.

Conclusions: These results can inform how we think about the potential for UCTs to improve the well-being of the poor.
Efficiency and Accuracy of Digital vs. Conventional Impressions for Implant Rehabilitations

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Impressions are taken in order to create a model that simulates the mouth of the patient when implants are desired to replace a missing tooth or teeth. The crown that the patient will permanently have in their mouth is fabricated directly from the stone model so the fit of the crown is very dependent on whether the impressions were accurate. Conventional impressions have been commonly used but Digital Dental Technology (DDT) has been in development since the 1980’s and digital impressions are quickly emerging as an alternative. The use of digital impressions for implant restorations allows doctors to make virtual assessments of the implant prosthetic space and see the depth of the restorative interface. There have been some studies that investigated the efficacy of digital impressions, but there is no literature that looks at the efficacy, accuracy, and clinical viability of implant restorations. Also, there is limited information on whether digital impressions provide benefits to the patients and/or dental practitioners. This project will set out to evaluate the efficiency (time-effectiveness) and accuracy (occlusal contacts, marginal fit, internal fit, and interproximal contacts) of taking a digital impression compared to conventional impressions for single implant restorations, as well as to evaluate the feasibility of a new technology in a clinical setting.

Thirty patients above the age of 21 with an osseointegrated single implant (to be restored) already existing in the posterior mandible or maxilla and intact adjacent/opposing dentitions (natural teeth or fixed permanent restorations) present were evaluated in this study. They then received impressions using the conventional approach and the digital approach (Cadent iTero digital impression system). The 60 impressions (2 for each patient) were used to create 60 stone models and fabricate 60 crowns. Each crown was then placed on the implant and occlusal contact and two contact points were analyzed using a tech scan. Following the treatment and analysis of which crown was a better fit, the patients will fill out questionnaires. This was a double-blinded study so the operator did not know whether the crown came from the conventional or digital impression.

Some of the patients have not yet been analyzed and the project is still in the process of being completed.
Policy Implications of the Bucharest Early Intervention Project: From Child Institutionalization to Family-Based Care

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Background: Global norms have long asserted that children have a right to family-based care. From the 1901 First White House Conference on Children in the U.S., to the 1989 UN Convention on the Rights of the Child, conventions call governments to replace congregate care “orphanages” or “asylums” with family-based alternatives. Yet despite purported consensus, an estimated 8 million children globally are still being raised in extended congregate care. Decades of observational studies document adverse outcomes among institutionalized children, but proponents of the practice still claim deficits stem from preexisting child characteristics.

The Bucharest Early Intervention Project (BEIP) remains the only randomized controlled trial to compare developmental outcomes among institutionalized children randomly placed in a pilot foster care program to outcomes among children randomized to stay in institutions pending availability of additional family placements. Now collecting age 12 follow-up data, the study has documented striking costs of institutional care in physical, intellectual, emotional, social, and neurophysiological development. It has also showed timing effects, as children placed into foster care at earlier ages have achieved greater recovery in many modalities.

Objectives: Numerous journal articles and an upcoming book have shared the BEIP’s scientific findings, but researchers have yet to analyze the significance of findings to global policy and practice. This project seeks to fill that gap. It undertakes policy analysis and generates an academic paper for publication in a peer-reviewed journal.

Methods: Methods first involved systematic compilation of BEIP scientific findings, and then synthesis of key policy lessons relevant to the 8 million children still suffering institutionalization. The study then offers in-depth discussion of challenges to changing policy and practice in complex settings globally, and considers how researchers may contribute to change.

Results: Several resounding policy implications emerged from BEIP findings. First, they suggest that institution-based child protection strategies impose devastating developmental costs on children, and that family-based alternatives can afford partial recovery. Interventions must reach children early to minimize lasting developmental impacts. Despite the complexity and challenges of global change, the BEIP supports contentions that there is no place in contemporary child protection policies for long-term child institutionalization.

Conclusion: While policy processes take place in complex sociopolitical spaces shaped by many non-scientific forces, findings from studies such as the BEIP have potential to promote change. In this case, findings may advance family-based protection strategies sensitive to the urgency of early intervention.
The Moral Economy of Violence in the US Inner City

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In an eight-week period, there were sixteen shootings with three fatalities, three stabbings, and fourteen additional “aggravated assaults” in the four square blocks surrounding our field site in the Puerto Rican corner of North Philadelphia. In the aftermath of the shootout that caused the most collateral damage, the drug sellers operating on our block were forced to close down their operations by several mothers who openly threatened to inform on them to the police. The goal of this paper is to analyze the social role of violence and to situate its value as a resource within the political economy and history of the US inner city.

This paper draws on fieldwork conducted from 2007-2012, primarily on two blocks selected because they were sites of active drug dealing in the area of Philadelphia identified as having the highest level of drug arrests in police statistics. We employed intensive participant-observer methods that entailed documenting personal observations in fieldnotes and recording unstructured, conversational audio interviews with individuals in the settings of their daily lives, in living rooms, on stoops and at family events and the street corners inhabited by drug dealers. Primary participants were three extended families that each spanned three generations. Additional interviews were conducted with the dozens of drug dealers who rotated fluidly through our field sites, the residents of these two blocks and institutional actors such as teachers, clinical staff and members of local political groups. Collected data was then thematically coded in Atlas.TI.

Our data was analyzed drawing on the concept of moral economy, reciprocal gift exchange, and a political economy critique of hypercarceralization in the US. We understand the violence we documented as operating within a moral logic framed by economic scarcity and hostile institutional relationships to the state. Residents seek physical and economic security as well as a sense of self-respect that oblige them to participate in solidary exchanges of assistive violence following kin-based and gender-scripted chains of allegiance. The value of violence is further elevated by the presence of a hierarchical, extractive drug economy filling the void left by inner city deindustrialization. Simultaneously, the spectacular visibility of interpersonal and criminal violence on inner city streets fuels national discourses of individual unworthiness and cultural sociopathy that enforce a de-facto US inner-city apartheid.
The Impact of High Deductible Health Plans on Utilization of Elective Orthopedic Surgery Procedures

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Escalation in health care spending in the United States has been a growing cause of concern in recent years. The US spends more on health care than any other developed nation, and the rate of spending growth has continued to outpace GDP growth. High deductible health plans (HDHPs), which feature annual deductibles of $1000 or more before most services are covered, are designed to increase cost-consciousness in patients, with a goal of decreasing unnecessary utilization in order to achieve cost savings.

With increasing pressure to control costs, HDHPs are becoming increasingly common. From 2005-2011, enrollment increased from negligible levels to 17% of the private insurance market. However, there is surprisingly little empirical data in the current era of HDHPs on how they impact care, and there is concern that these plans also might prevent desired or necessary care for some populations. Most of the evidence is limited to short term studies with data from a single carrier or employer, impairing generalizability. In addition, there are no data the impact of HDHPs on the utilization of discretionary procedures.

In this study, we examine the impact of these HDHPs on elective, patient-driven orthopedic knee procedures. Visits related to knee pain are common and costly, and untreated knee problems can have substantial impacts on functional status and quality of life. Using the Truven MarketScan database, containing health encounter information on 25 million individuals from 2007-2011, we empirically identified individuals enrolled in an HDHP, and further identified those individuals whose entire firm was switched from a traditional plan to an HDHP during the experimental period, and utilized propensity score matching to generate a control dataset. We will employ a quasi-experimental difference-in-differences design wherein we collect data on utilization of services in a baseline year while enrolled in a traditional plan, and then in the subsequent year we will follow individuals as they either remain in a traditional plan or switch into an HDHP. We will identify the impacts of plan type on utilization through ascending levels of care by comparing those who remain in the traditional plan with those who switch to the HDHP. We will first identify those patients with an office visit to a PCP for a knee-specific diagnosis, and track visits to orthopedists, imaging services, minor office-based procedures such as therapeutic injections, and major surgical procedures. We hypothesize that enrollment in an HDHP will deter utilization at each of these points.
Test-Retest Reliability and Technical Validity of Spontaneous EEG Microstate Analysis

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BACKGROUND: The pathophysiology of several neuropsychiatric illnesses is associated with neurophysiological impairments. Longitudinal monitoring of the brain's neurophysiological health may therefore offer a valuable illness management strategy. To achieve this, we need cost-effective and reliable neurophysiological biomarkers suitable for translation to clinical practice. Resting-state electroencephalography (EEG) is an inexpensive electrophysiological tool that may yield reliable biomarkers. One EEG analysis approach describes EEG as a dynamical system defined by its state – the combination of variables that describe the system at each instant – and dynamics – how the state evolves over time. EEG microstate analysis is one such method. In microstate analysis, the state is defined by the topography of electric potentials plotted over the multichannel array. These states are clustered into 3-5 classes, called microstates. Features of microstate dynamics include average microstate duration and frequency, fraction of total time covered by each microstate, and transition patterns among microstates. Microstate features integrate data from all electrodes and may indicate the brain's functional connectivity and network integrity. Indeed, prior studies demonstrated specific microstate impairments in neuropsychiatric illnesses including schizophrenia and Alzheimer's disease. However, the use of microstates as neurophysiological biomarkers requires assessment of the methodological validity and test-retest reliability of microstate features.

METHODS: We analyzed resting-state, eyes-closed, 30-channel EEG from 10 healthy subjects over 3 sessions spaced at least 48-hours apart. We identified four microstate classes and calculated the average microstate duration, frequency, coverage, and transition probabilities. We then examined: 1) the test-retest reliability of microstate features across sessions; 2) the features’ consistency between two common microstate clustering methods, TAAHC and k-means clustering; and 3) the features’ consistency between 30-, 19-, and 8-electrode arrays. We employed Cronbach’s α and the standard error of measurement (SEM) as indicators of test-retest reliability and consistency across methods.

RESULTS: All microstate features had high test-retest reliability across sessions (Cronbach’s α > 0.7, SEM = 10% of mean values). All but one feature had consistency across methods (Cronbach’s α > 0.9). The four microstate classes identified in 30-channel data were also identified in 19- and 8-electrode arrays, and all features had high consistency across arrays (Cronbach’s α > 0.9), indicating that as few as 8 electrodes may be sufficient for microstate analysis.

CONCLUSIONS: High test-retest reliability and cross-method consistency of microstate features suggests their potential as biomarkers for assessment of the brain's neurophysiological health. Future studies should further document the reliability and validity of microstate analysis across behavioral states.
Crossing Rivers and Climbing Mountains for Healthcare: Exploring Changes in Health Service Utilization in Neno District Malawi

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Ranking 171st out of 182 countries on the Human Development Index, the southern African nation of Malawi is one of the poorest countries in the world. As is common in other parts of the globe, poverty is most severe in the rural areas that serve as home to more than 80% of the population. In solidarity with the Malawian Ministry of Health (MOH), Partners In Health (PIH) established Abwenzi Pa Za Umoyo (APZU) in the rural district of Neno to provide comprehensive health services to some of those most in need. Since APZU’s arrival in 2007, outpatient (OPD) visits to the 13 health facilities in Neno District have more than doubled. The underlying cause of increased health care utilization in Neno is unclear.

The goal of this study was to identify the factors associated with the observed increase in health service utilization in Neno. Understanding these factors is critical in developing pragmatic interventions to sustain access to care as well as to advocate for resources needed for the patient population.

A mixed methods approach was used to understand drivers of increased health care utilization. Existing health service usage data routinely reported to the MOH was reviewed for antenatal care, under-5 care, outpatient treatment, and inpatient treatment from 2005 to 2012. Descriptive analyses were used to elucidate patterns of health care use over time, across different APZU-supported health centers, and at the district level. Semi-structured focus groups with health care system users were conducted to explore drivers for increased health service utilization, and thematic content analysis was used for qualitative data analysis.

On the district level, OPD use more than doubled from 2007 to 2012, whereas antenatal care and under-5 care saw more modest increases of 11% and 52% respectively. Within Neno, the highest increases in OPD attendance occurred in health facilities that had the greatest infrastructural improvements while the smallest rises occurred at sites that maintained outpatient user fees. Among health facility users, eliminating fees, bringing health services closer to the community, and maintaining well-stocked drug supplies were the most frequently noted facilitators to increase health service use. Distance, fear of learning HIV status, and cost were noted as the greatest barriers to seeking healthcare.
Investigation of Factors Affecting Completeness of National Trauma Data Bank Reports

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Data entry into the National Trauma Data Bank (NTDB) is required for American College of Surgeon’s Trauma center designation. However, only essential criteria are mandatory, such as mortality. Thus, trauma report completeness varies from center to center. Resource constraints, including statewide trauma system implementation, may account for to the incomplete entry of certain centers into the NTDB. A thorough examination of the factors that enhance completeness of the reports is much needed in order to improve the usefulness of NTDB in assessing clinical outcomes. We hypothesize that centers within a statewide funded trauma system will have higher completeness of NTDB entries.

We plan to compare NTDB report completeness in states that have non-funded statewide trauma systems to those with funded systems. We will compare how intermittent funding affects a given state on NTDB report completeness. We will separate reports into two categories: report from trauma centers in states with funded statewide systems and those without a funded statewide system. We will develop a composite completeness score, by identifying the top five most reported and the five least reported entries (both which are non-required information). We will give each entry a value and compare the total score of each hospital. This will allows us to examine more than one entry and minimize biases. Using the American Hospital Association Database we will stratify our results based on additional confounders including hospital size, rural vs. urban, location and ownership just to name a few. We also interested in states that choose states undergone changes in trauma system funding over extended slices of time such as 5 and 10 year intervals.
Characterizing the role of the alternative complement pathway in vascular regression in a mouse model of retinopathy

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Abnormal blood vessel growth in the retina can impair vision and lead to blindness. Several forms of retinal disease (e.g., retinopathy of prematurity, diabetic retinopathy) exhibit this phenomenon, which often progresses in two distinct phases: initial vascular regression (Phase I) and subsequent pathological neovascularization (Phase II). Interestingly, vascular regression coincides with a spike in immune activity, and recent studies have found a link between the complement system, a key part of the innate immune system, and certain vaso-proliferative retinopathies (e.g., age-related macular degeneration).

However, the role and mechanism of how the complement system influences retinopathies remains unclear, particularly for the early stages of disease. Thus, I tested our lab's hypothesis that the complement system mediates vascular regression in the early stages of retinopathy in a mouse model of oxygen-induced retinopathy (OIR). Given the time constraint, difficulties in breeding complement knock-out mice, and variability in the OIR model, I focused specifically on alternative pathway knockout mice (Fb−/−), since this pathway exhibits constitutive activity and does not rely on pathogen-binding antibodies. Utilizing Fb−/− mice and age-matched C57Bl/6 (control) mice, I sought to uncover the role of the alternative complement pathway in Phase I of retinopathy (i.e., vascular regression) and to identify the source of complement factors in the retina during this disease phase.

In order to test this hypothesis, I examined mouse retinas via fluorescence microscopy after lectin staining of the retinal vasculature. Postnatal day (P) 8 was chosen because vascular regression is most prominent after 24 hours of oxygen exposure. Adobe Photoshop was used to outline and quantify the area of vaso-obliteration (VO). In order to localize the source of complement factors in the retina, retinal layers were isolated from P8 OIR C57Bl/6 mice and P8 non-OIR (normoxic) C57Bl/6 mice using laser capture microdissection. Quantitative real-time polymerase chain reactions were then run in order to analyze the mRNA content for the identification and quantification of complement gene expression in different retinal cell types (results and analysis pending).

Comparing P8 wild-type mice undergoing OIR (n=8) to the alternative knockout mice (n=10), the alternative pathway mice exhibited less VO than wild-type mice (mean VO% ± SE, 40.93% ± 1.08% vs. 44.28% ± 0.90%, p < 0.05), which is consistent with our hypothesis. These results implicate the involvement of the alternative complement pathway in vascular loss, found in the early stages of retinopathies.
Identification of Potential Microbial Contributors to Crohn’s Disease and Aspirin Exacerbated Respiratory Disease

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Background: The pathogen discovery team at Dana Farber and the Broad Institute has created a genomics-based approach to the discovery of pathogens called PathSeq. PathSeq entails whole genome or total RNA sequencing of diseased or control human tissue, followed by computational subtraction of human sequences, and finally taxonomic classification of all non-human sequences. Analysis of these classified sequences may lead to the identification of candidate pathogens. Further analysis of unclassifiable reads by de novo assembly can lead to the discovery of potential novel, yet undiscovered candidate pathogens.

Using this approach to pathogen discovery, Dr. Ami Bhatt and colleagues looked for microorganisms of interest in samples of Crohn’s disease. Crohn’s disease is an inflammatory bowel disease that can cause diarrhea and malabsorption among other morbidities. After genomic analysis of microorganisms in a set of ileal biopsy specimens from patients with Crohn’s disease and normal controls, Dr. Bhatt’s team found an increased presence of Mycobacterium abscessus in cases.

I am also collaborating with an immunology research team at the Brigham to investigate causative organisms of aspirin-exacerbated respiratory disease (AERD). AERD has an unknown etiology and can cause severe asthmatic reactions to COX-1 inhibitors.

Methods: To investigate the association M. abscessus may have with Crohn’s, I designed a PCR-based assay to query the presence of M. abscessus using the NCBI BLAST algorithm.

To investigate microbiome of AERD, nasal polyp tissue from cases and controls were collected. Samples were preserved in RNALater solution immediately upon polypectomy and were flash frozen.

Results: Generated primers specific to M. abscessus were validated by performing PCR on gDNA extracted from M. abscessus and M. tuberculosis. PCR demonstrated amplification of the target sequence in M. abscessus but not M. tuberculosis gDNA, demonstrating primer specificity. Primers amplified M. abscessus down to a gDNA amount of .002ng, demonstrating primer sensitivity.

Bioanalyzer analysis of RNA extracted from three fresh AERD nasal polyp samples show high quality RNA.

Conclusions: The next step is to collaborate with colleagues at Mount Sinai Hospital to see if our primers detect the presence of M. abscessus in their Crohn’s disease colon biopsy samples. AERD sample acquisition is ongoing. Once a total of six AERD samples have been collected, bar-coded sequencing libraries will be generated from the total RNA that is obtained, in order to perform total RNA sequencing using the Illumina V3 sequencing platform. The resulting data will be analyzed using PathSeq to detect candidate microbial triggers.
Accuracy of Digital Impressions in the Milling of an Implant Crown

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The accuracy of digital impressions and the milling of implant crowns greatly influences the clinical viability in implant restorations. The aim of this study is to calculate the propagation of error in the process of milling an implant crown.

Thirty digitally milled models impressed directly from a reference model were prepared. The models were scanned by a laboratory scanner and 30 STL datasets from each group were imported to an inspection software.

In each analysis, STL datasets were aligned by a repeated best fit algorithm and 18 specified contact locations of interest were measured in mean volumetric deviations. The master reference dataset was aligned to the master reference dataset thirty times to determine the software variation. The thirty reference datasets were aligned to the master reference dataset to determine the scanner variation. The thirty milled model datasets were aligned to the master reference dataset to determine the milling variation. The 18 specified contact locations of interest were pooled by cusps, fossae, interproximal contacts, horizontal and vertical axes of implant position and angulation. The pooled areas were statistically analyzed by comparing each group to the reference model to investigate the mean volumetric deviations accounting for accuracy and standard deviations for precision.

Software and scanner variation were negligible. Milled models from digital impressions had comparable accuracy to digital models. However, differences in fossae and vertical displacement of the implant position from the digitally milled models compared to the reference model, exhibited statistical significance (p<0.001, p<0.020 respectively). Further statistical analysis is needed to calculate the propagation of variation in the milling process. The process used two different scanning technologies. A model will need to be created to relate the two scanners.

This study is one of the first studies that investigate the accuracy of the milling process as it applies to the implant restoration. The volumetric deviations may not be interpreted as the “truth” of the absolute difference of a specific location of one model compared to another. However, the pooled locations describe the reliability of the milling process as it applies to specific anatomic locations on the tooth.
Intratumoral heterogeneity and tumorigenicity: Characterizing Progenitor Cells

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While most human tumors are derived from a single cell, genetic and epigenetic alterations within the tumor cell population generate considerable intratumoral heterogeneity. Despite our knowledge of the existence of tumor cell heterogeneity and the processes that create it, the functional consequences on tumor progression have not been feasible to characterize because of the inability to culture clonal populations of tumor cells from patients. As part of a larger collaboration, we have developed a protocol for culturing luciferase-secreting clonal populations derived from primary ovarian carcinomas. *In vivo* experiments demonstrate a striking heterogeneity in the ability of the clonal populations to initiate tumors, with only one clone (Clone 31) showing robust tumor formation *in vivo*. Interestingly, this clonal population was strikingly heterogeneous containing epithelial colonies as well as spindle shaped cells with a more mesenchymal-type morphology, suggesting that clone 31 may have been a progenitor cell.

To examine the phenotypes of the distinct populations of cells within Clone 31 and to characterize their tumor-initiating abilities, we generated subclonal populations of Clone 31. First, we tested their ability for anchorage-independent colony formation in agar. The subclones exhibited a great heterogeneity in their ability to proliferate in soft agar, as well as in the size of colonies generated. For the remainder of the study, we focused on eight subclones; chosen to be representative of the variability of morphology and colony-formation activity in agar.

The eight subclones were diverse in their morphology, ranging from mostly epithelial to mostly mesenchymal. Their proliferation rate also varied with doubling times ranging from 25 to 53 hours and did not correlate with morphology or soft agar colony formation. Invasiveness in a three-dimensional basement membrane assay ranged from 24 to 65 percent.

The *in vivo* study demonstrated variability in tumor initiation between the subclones. Five of the subclones expanded at a faster rate than the parental and Clone 31 over 10 weeks. Two of the subclones did not proliferate and the last one surpassed the parental, but not Clone 31 over 10 weeks.

The findings thus far demonstrate that the progeny of Clone 31 is functionally heterogeneous, supporting the conclusions that these cells are generated by both differentiation and self-renewal of a progenitor cell. To elucidate the mechanism of cell renewal and differentiation between clone 31 and its progeny, RNA sequencing will be undertaken in the next phase of the experiment.
Assessment of Quality of Care for Non-Communicable Diseases in PIH-supported Health Centers in Rural Rwanda

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Introduction: In collaboration with the Ministry of Health (MOH), PIH has developed robust protocols and trained nurses for clinical management of uncomplicated Non-Communicable Diseases (NCDs), particularly Diabetes (DM), Hypertension (HTN), and Chronic Respiratory Diseases (CRD), at health centers (HC) in rural Rwanda. Monitoring and evaluation is necessary to identify persistent gaps in care and to drive internal quality improvement. Using the Mentoring and Enhanced Supervision at Health Centers (MESH) checklists, we assessed quality of care (QOC) at 5 HCs in Kayonza and Kirehe Districts.

Methods: Experienced nurse-mentors were asked to complete checklists for DM, HTN, and CRD during routine clinical observations at the HCs. We compiled 51 checklists (26 for HTN; 15 for CRD; 12 for DM) at five HCs: Kabarondo, Ndego, Mulindi, Rusomo, and Nyarubuye. We determined percent of “Yes” responses to five pre-selected questions, common among checklists: History- Did the provider ask about missed medication doses?; Physical Exam- Did provider check and document blood pressure?; Counseling- Did provider counsel the patient about disease and lifestyle choices?; Treatment- For patients not being admitted, did provider make appropriate outpatient medication adjustments (in concordance with mentor?); Communication- Did provider communicate next appointment date?

Results: Across all sites, providers asked HTN patients about missed medication doses in 77.3% of cases; checked and documented blood pressure in 91.3% of cases; counseled patient about their disease in 66.6% of cases; prescribed the correct outpatient medications in 91.6% of cases; and communicated next appointment date in 87.0% of cases.

Providers asked DM patients about missed medication doses in 66.6% of cases; checked and documented blood pressure in 75% of cases; counseled patient about their disease in 33.3% of cases; prescribed correct outpatient medications in 83.3% of cases; and communicated next appointment date in 100% of cases.

Providers asked CRD patients about missed medication doses in 64.3% of cases; checked and documented blood pressure in 53.3% of cases; counseled patient about their disease in 20% of cases; prescribed the correct outpatient medications in 100% of cases; and communicated next appointment date in 92.3% of cases.

Conclusions: CRD has the lowest percentage of “Yes” responses in 3 of the 5 categories. Among the variables, Counseling has the lowest percentage of “Yes” responses in all 3 diseases. Underlying reasons for these gaps should be discussed with the NCD team, including HC nurses, and systems issues (eg, missing equipment) addressed. These findings can also guide future nurse trainings.
Caregiver Medical Traumatic Stress in Newly Diagnosed Pediatric Cancer Patients: 
Associated Psychosocial Variables and Implications

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Background: The diagnosis and treatment of pediatric cancer is a stress-provoking event that has pervasive implications for the entire family, especially the child’s caregivers. Studies have shown that caregiver stress can adversely affect family functioning, coping, long-term adjustment, and the patient’s quality of life.

Families carry different psychosocial risk factors that may affect their ability to effectively cope with stress. The Psychosocial Assessment Tool (PAT 2.0) is a quantitative measure of psychosocial risk for families of newly diagnosed pediatric cancer patients. The PAT assesses family functioning across several subscales, including “Structure and Resources” and “Caregiver Medical Traumatic Stress (CMTS)” so that clinicians can both classify families by psychosocial risk and intervene accordingly.

CMTS, distinct from “stress” as a general construct, is defined as a caregiver’s psychological and physiological responses to the full spectrum of their child’s illness/treatment. Considering the clinical importance of CMTS and its contribution to a family’s psychosocial functioning, this project examines:

1) The association between CMTS and (a) Other PAT subscales and (b) Total PAT score
2) Whether group membership into stratified CMTS levels is predicted by other PAT subscales

Methods: Thirty-nine caregivers of children with hematologic, neurological, or solid tumor malignancies consented to participation in the study, which included a medical record review for the PAT. Bivariate, Pearson correlations were run between each of the PAT subscale scores and between the PAT subscales and “Total PAT Score.” A Linear Discriminant Analysis examined the interaction between PAT subscale scores and CMTS group membership.

Results: A strong, positive correlation existed between CMTS and “Structure and Resources,” (r(N=39)=0.38, p<0.02). CMTS (r(N=39)=0.62, p<0.01) and “Structure and Resources” (r(N=39)=0.57, p<0.01) were two of the strongest correlators with “Total PAT Score.” The only subscale which predicted CMTS group membership was “Structure and Resources,” Wilks’ Lambda=0.59, F(3,33)=7.80, p<0.01.

Discussion: The strong correlation between CMTS and the “Total PAT Score” suggests that interventions aimed at ameliorating a caregiver’s stress response have potential to decrease a family’s psychosocial risk. “Structure and Resources” emerged as a crucial variable that may potentially predict CMTS and overall psychosocial risk. Therefore, addressing deficits in a family’s access to resources might aid in both short-term and long-term adjustment. Even when deficits in resources are not easily remedied, this variable identifies families who might benefit from increased psychosocial services. Future studies might investigate potentially causal relationships between CMTS and other psychosocial variables and evaluate the efficacy of psychosocial interventions.
Retrospective Assessment of Patient Satisfaction After Orthognathic Surgery

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Orthognathic surgery to correct dentofacial deformities is not without risks, including lack of patient satisfaction. It has been reported that post-operatively, patients tend to exhibit dissatisfaction pertaining to biting (62%), chewing (55%), numbness (53%), and facial swelling (34%). To improve upon the success rate of orthognathic surgery, it is beneficial to have knowledge of how post-operative patients perceive their overall results. The purpose of this study was to assess patient satisfaction with (1) appearance, (2) functional abilities, (3) general health, (4) sociability, and (5) patient-clinician communication after different orthognathic surgeries.

We hypothesize that there will be greater overall satisfaction seen in patients who have undergone single jaw surgery (LeFort I osteotomy or bilateral sagittal split osteotomy [BSSO]) as opposed to double jaw surgery. We also hypothesize that jaw/bite force functionality will be the strongest determinant of overall satisfaction. By gaining knowledge of the relationship between overall satisfaction and satisfaction pertaining to different aspects of the patients’ lives, inferences can be made to improve upon the procedural techniques and to make the recovery process a less disturbing experience for patients.

A sixteen-question survey was developed and each question was placed into one of five categories (listed above) that pertain to assessing overall patient satisfaction. It will be administered at 6 months or 1 year after orthognathic surgery to fifty patients at the University of Pennsylvania and Massachusetts General Hospital. A patient information survey will also be administered to the subjects in order to account for any confounding variables.

The results of this study are currently incomplete and the study will be continued throughout the fall and winter. Data has been obtained for nine subjects thus far. Once all of the data is collected, statistical calculations will be performed to examine the significance of each aspect of the patients’ lives in terms of determining their overall satisfaction with the procedure. Correlational studies will also be performed to determine whether there is an association between patient satisfaction and the type of orthognathic surgical correction undergone.
Advancement of Patient-Centered Medical Homes under Oklahoma Medicaid Program from Entry to Optimal Level: Barriers and Incentives.

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The patient-centered medical home (PCMH) is a team-based model of care that seeks to improve quality of care and control costs. The Oklahoma Health Care Authority (OHCA) directs Oklahoma’s Medicaid program and contracts with 861 medical home practices across the state in one of three tiers of operational capacity: Tier 1 (Basic), Tier 2 (Advanced) and Tier 3 (Optimal). Only 13.5% (n=116) homes are at the optimal level; the majority (59%, n=508) at the basic level.

In this study, we sought to determine the barriers that prevented Tier 1 homes from advancing to Tier 3 level and what incentives would motivate providers to advance from Tier 1 to 3. Our hypotheses were that Tier 1 medical homes were located in smaller practices with limited resources and the providers were not convinced that the expense of advancing from Tier 1 status to Tier 3 status was worth the added value.

We analyzed OHCA records to compare 508 Tier 1 (entry-level) with 116 Tier 3 (optimal) medical homes for demographic differences with regards to location: urban or rural, duration as medical home, percentage of contracts that are group contracts, number of providers per group contract, panel age range, panel size, and member-provider ratio. We surveyed all 508 Tier 1 homes with a mail-in survey and focused follow up visits to identify the barriers to and incentives for upgrading to Tier 2 or 3.

We found that Tier 1 homes were more likely to be in rural areas, run by solo practitioners, serve exclusively adult panels, have smaller panel sizes, and higher member-to-provider ratios in comparison with Tier 3 homes. Our survey had a 35% response rate. Results showed that the most difficult changes for Tier 1 homes to implement were providing 4 hours of after-hours care and a screening, intervention and referral program for mental illness and substance abuse. The results also showed that the most compelling incentives for encouraging Tier 1 homes to upgrade their tier status were less red tape with prior authorizations, higher pay, and help with panel member follow-up.

We concluded that multiple interventions will help medical homes in Oklahoma advance from the basic to the optimal level including sharing of resources among adjoining practices, expansion of OHCA online resources to help with pre-authorizations and patient follow up and the generation and transmission of data on the benefits of medical homes.
Multiphoton photoconvertible probe for in situ labeling of circulating cells

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In recent years, photoconvertible probes have been used in numerous biomedical applications including in situ cell labeling, protein tracking and super-resolution imaging. Multiphoton photoconvertible probes are of particular interest due to their abilities to selectively label cells in three dimensions and highlight cells located deep in tissue. However, most conventional photoconvertible probes suffer from inefficient two-photon absorption. We have observed that the fluorescence of a number of cyanine-based fluorophores blue-shifts with multiphoton activation. In particular, a common nucleic acid stain, SYTO 62, photoconverts extremely efficiently and is used to label circulating cells in situ. To our knowledge, this is the first photoconvertible fluorophore demonstrated for in vivo multiphoton microscopy.

Photoconversion and multiphoton imaging was conducted using a custom-built video-rate multiphoton microscope. SYTO 62 was characterized prior and following photoconversion by absorption and emission spectroscopy, high performance liquid chromatography (HPLC) and mass spectrometry.

With photoconversion, the red fluorescence of SYTO decreases nearly 90%, while the green fluorescence increases over ten-fold, corresponding to a 100 fold increase in the green/red emission ratio. SYTO photoconverts in approximately 4 ms per cell at a laser power not causing cell phototoxicity. HPLC and mass spectrometry analysis suggest the major mechanism of photoconversion is bond cleavage. The green fluorescence of photoconverted SYTO was stable over 24 hours in HeLa cells in vitro. Real-time in situ labeling of circulating leukocytes was achieved in cortical venules of mice.

SYTO 62 stained cells can be photoconverted and imaged efficiently at a single near-IR wavelength, providing improved convenience over previously reported photoconvertible probes. The photoconversion lifetime of SYTO far exceeds that of traditional photoconvertible proteins. SYTO is among the most rapidly photoconverting probes reported in the literature. These unique properties of SYTO along with its suitability as a multiphoton probe make it an ideal candidate for in vivo cell tracking experiments. SYTO 62, a cyanine-based fluorophore, is an attractive alternative to photoconvertible proteins, especially when transgenic mice or stable transfection of cells are not feasible. We expect SYTO 62 and other related dyes to open new possibilities of research in studying cell migration, regeneration, and embryogenesis.
Monitoring craniofacial development using time-lapse imaging in *Xenopus laevis*

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The face is a critical component to how we engage with our environment and how others perceive us. However, 1/1600 live births has some level of craniofacial anomaly. One of the most common defects is cleft lip and/or cleft palate, which effects as many as 10/1000 live births and carries a lifetime cost of over $100,000. Some of these defects are attributed to genetics, but others are believed to have a non-syndromic root, such as teratogens or vitamin deficiency. However we still have a lot to learn about the mechanisms behind these defects.

In order to better visualize the events that lead to these abnormalities, we chose to employ time-lapse imaging of live animal models to provide insight into the nuance of morphological changes during development. By capturing these subtle changes of face and mouth formation, we can better distinguish normal from abnormal development.

In the study of craniofacial development, the *Xenopus laevis* has been a valuable vertebrate model for two reasons: 1) The relatively short time frame of facial development (from fertilization to mouth opening is under 72 hours). And 2) the ease of manipulation since the phenotype can be manipulated in vitro. However, imaging of live *Xenopus* presents certain challenges when it comes to keeping the specimen in a precise position for an extended duration, as well as keeping the specimen in focus while it is growing. In order to address these challenges, we have adapted previous methods of specimen preparation in order to allow for time-lapse imaging.

We used the time-lapse features from the ZEN software that accompanies the Zeiss Discovery.V8 bright field microscope. The wild-type *Xenopus* embryos were suspended in 1% agar solution within the wells of 2% agar plates in order to balance visibility and support, respectively. The dish was then filled with an MBS solution in order to keep the environment moist and to provide an even field of view. Images were taken at 6-minute intervals and collected over a total of about 48 hours (4x 12-hour intervals). Data was then aligned within the ZEN program, cropped and color-corrected within Photoshop, and then compiled using iMovie.

The development of this imaging protocol using wild-type embryos provides a foundation for future inquiry of abnormal craniofacial development, and will hopefully serve basis for tracking neural crest cell migration.
Modern Orthognathic Surgery: Has There Been a Shift in Demographics?

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Orthognathic surgery is the treatment of choice to restore a functional occlusion in patients with discrepancies in jaw position. It has most commonly been a treatment rendered in the second or third decade to correct skeletal malocclusions not amenable to orthodontic treatment alone. In addition to its effects on occlusion, it also can provide significant aesthetic benefit, restoring facial proportions and harmony.

Recently, there seems to be an increase in older patients undergoing orthognathic surgery. Much of the increase may be due to the success of maxillomandibular advancement in treatment of patients with obstructive sleep apnea. Subjectively, another subset includes older patients seeking an aesthetic improvement, particularly those over 40. However, both the current and historic literature consider older patients to be in their thirties and include few patients in their forties, fifties, or sixties. Data obtained from these studies may not be applicable to patients in their forties or older.

The purpose of this study was to assess how the demographic of orthognathic surgery patients has changed over time, evaluate motivation to seek treatment, and compare outcomes between patients over and under 40. We hypothesized that within patients over 40, males primarily seek treatment for functional problems while females primarily seek aesthetic improvements. We also hypothesized that older patients would have increased rates of hardware removal and permanent paresthesia as well as longer hospital stays.

A total of 942 patients undergoing 1377 procedures at Massachusetts General Hospital were included in the study. The predictor variables were time period, age, sex, and race. When time period was the predictor the primary outcome variable was age. When age was the predictor the primary outcome variable was motivation to seek treatment. Secondary outcome variables included incidence of hardware removal, incidence of paresthesia, and length of hospital stay.

Patients over 40 comprised 13.8% of the study sample. Males were more likely to seek treatment for functional problems while females were more likely to seek aesthetic improvements. Patients over 40 had 2-5 times greater risk of hardware removal compared to patients under 40. Patients over 40 also had significantly higher rates of permanent paresthesia and longer hospital stays.

This study demonstrates that while patients over 40 make up a significant portion of the patient population, operating on this demographic carries greater postoperative risk. A better understanding of how age impacts surgical expectations and outcomes will improve patient satisfaction in this growing demographic.
A Critical Period for Neuromuscular Junction Re-Establishment and Functional Recovery After Peripheral Nerve Injury in the Mouse

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Repair of peripheral nerve injury in humans often results in poor functional motor recovery, depending on the location and the timing of surgery. This deficit in motor recovery has previously been attributed to the failure of axons to regenerate into the target muscle. However, our lab has previously reported that following sciatic nerve transection and immediate resuture in mice, regenerating axons are observed at the motor endplate even in animals with poor functional recovery. In this model, motor recovery reaches a plateau approximately 35 days post-injury, with no further recovery beyond this period.

Based on this observation, we proposed that following axonal injury, there is a critical period during which the axon must reach the target muscle in order to form a functional neuromuscular junction. To test this, we have developed a mouse model of differential prolonged denervation, in which the proximal sciatic nerve is crushed repeatedly every 2 to 7 days, preventing regenerating axons from reaching the target muscle. This multiple crush model allows us to vary the period of denervation, by modifying the number of crushes. We performed 3, 4, or 5 crushes every 7 days (corresponding to ~24, 31, or 38 days of denervation, respectively) and assessed functional motor recovery using the toe-spreading score, modified sciatic function index, dynamic weight bearing, and hindlimb grip strength.

Motor recovery occurs after 3 or 4 multiple crushes (24 or 31 days of denervation) but not after 5 crushes (38 days). Labeling of muscle tissue with alpha-bungarotoxin and anti-neurofilament antibody demonstrated presence of axons at motor endplates in all 3 groups. Thus following prolonged denervation > 38 days, a functional motor deficit persists despite muscle reinnervation.

Although the mechanism for the motor deficit requires investigation, these results suggest that functional neuromuscular junction reestablishment following nerve injury requires more than anatomical reinnervation of the motor endplate.
Cost Effectiveness Analysis of Silver Wound Dressing in Lower Extremity Wounds

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Surgical site infections persist as one of the most common post-operative surgical complications, occurring in approximately 2% of surgical procedures and resulting in a substantial economic burden on the healthcare system. Wounds following lower limb revascularization are particularly prone to infection and dehiscence. Although silver has been implicated as an antimicrobial agent for fighting bacterial resistance, conclusive evidence as to its efficacy on post-surgical infection outcomes is lacking. Furthermore, no substantive cost-effectiveness analyses exist comparing post-operative care using silver-containing wound dressings versus non-silver eluting dressings.

The purpose of this study is to determine the cost-effectiveness of Acticoat Absorbent silver-containing wound dressing compared to conventional non-silver containing gauze for post-operative wound care following lower extremity revascularization procedures. This analysis supplements an ongoing multi-center randomized controlled trial (RCT) comparing the efficacy of Acticoat dressing and gauze in reducing such post-operative infection rates. We hypothesize that use of Acticoat as the post-operative dressing will be more cost-effective than use of non-silver eluting gauze dressing following lower extremity revascularizations.

To test this hypothesis, we obtained Brigham and Women’s Hospital (BWH) cost data and matched the data to the patients included in the aforementioned RCT. The primary endpoint of our analyses is the total 30-day cost of post-operative revascularization-related care in the treatment patients versus control patients. Determination of cost-effectiveness relies on separate determination of both cost from BWH’s cost data and effectiveness from the aforementioned RCT, and then setting these two components in a final cost-effectiveness ratio.

As the RCT is still ongoing, final cost and effectiveness data are projected to be available by the end of October. Using SAS statistical software, preliminary work has been done to sort and match BWH cost data with the RCT patients and to determine relevant post-procedural costs. As the final data are made available, post-operative revascularization-related costs, complication frequencies, and cost-effectiveness ratios will be determined for the entire cohort of treatment and control patients. Subanalyses will determine whether certain patient subgroups demonstrate greater cost-effectiveness for the silver dressings than do other groups. Finally, factors affecting increased costs will be determined, and sensitivity analyses will be performed to determine how changes in critical components of the study, such as factor price, affect the cost-effectiveness results.

The final data will inform clinical standards and contribute to more cost-effective practices for vascular surgery post-operative care.
Towards a molecular basis of tissue heterogeneity in mitochondrial disease

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Mitochondrial diseases are clinically heterogeneous set of disorders characterized by respiratory chain dysfunction. They affect at least 1 in 5,000 live births and can present from infancy to adulthood, involving either multiple organ systems or manifesting in a highly tissue specific fashion. The clinical hallmarks include myopathy, cardiomyopathy, lactic acidosis, ataxia, seizures, blindness, neuropathy, GI dysmotility, and liver failure.

Although more than 150 mitochondrial syndromes have been described to date, little is understood about the molecular basis of the tissue-specific variability of these diseases. For example, the same m.3243A>G mutation in MT-TL1 can cause mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome in some families, while, for unknown reasons, in other families it causes cardiomyopathies or maternally inherited diabetes and deafness (MIDD).

Here, we describe an approach for inferring cell- and tissue-specific factors that modulate sensitivity to mitochondrial lesions. For 224 cell lines, we downloaded and analyzed gene expression and mutational profiles, as well as performing drug screens to measure responses to eight drugs known to cause mitochondrial dysfunction. These eight drugs include inhibitors of mitochondrial translation, mtDNA replication, redox balance, and oxidative phosphorylation. Genomic markers for cell- or tissue-specific factors are then identified by creating linear models, both across and within tissues-of-origin.

Our analysis has highlighted expression of known molecular targets of the drugs and glycolytic genes as predictors of drug sensitivity. In addition, novel genes and pathways not previously implicated in modulating the cellular and metabolic response to mitochondrial dysfunction are inferred as markers.
Risk of Brain Metastases in Stage IIIA/IIIB Non-small Cell Lung Cancers Treated With Definitive Radiation

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Lung cancer is the leading cause of cancer-related mortality, responsible for over 150,000 annual deaths in the United States. About eighty percent of these cases are non-small cell lung cancer (NSCLC). The prognosis is particularly poor for NSCLC patients with locally advanced tumors, stage IIIA or IIIB. The five year overall survival for locally advanced patients is estimated at 23%, and locoregional recurrence rates range from 20 to 50 percent in randomized control trials. The optimal treatment for these patients remains controversial.

Patients with locally advanced NSCLC have a high risk of distant relapse, with the most common site of metastasis being the brain. Various studies have investigated the risk of brain metastasis in locally advanced NSCLC. Robnett et al found a crude risk of 19% and a 2-year actuarial risk of 30% in 150 patients treated with chemoradiation from 1992 to 1998. Mamon et al analyzed 177 patients with stage IIIA NSCLC from 1988 to 2000 receiving surgical resection and found that 34% had the brain as site of first distant metastasis.

However, these studies have sample size limitations. Additionally, no analyses of brain metastasis risk have been performed for patients treated using modern radiation techniques and chemotherapy regimens. We performed a retrospective analysis of brain metastasis risk in 654 patients with NSCLC treated with radiation therapy with curative intent at our institution, Brigham and Woman’s Hospital. The Cox Proportional Hazards model was used for statistical analysis, with survival analysis beginning at the patient’s first head staging CT or MRI. Patients were censored at time of death or at relapse in another distant metastatic site.

Data analysis is in progress. We plan to analyze both the crude and the actuarial risk for brain metastases in our patient cohort. We will also tabulate the number of brain metastases each patient presented with (single vs multiple) and what treatment the patients received for their brain metastases. Furthermore, we will perform subgroup analyses comparing brain metastasis risk for patients with different types of histology (ie adenocarcinoma vs squamous cell) and for patients who received a carboplatin/taxol regimen vs a cisplatin/etoposide EP50/50 chemotherapy regimen.
Health Weight Intervention (HWI) Pilot Study in the Pediatric Dental Setting

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In the past 30 years, rates of childhood obesity have increased quickly leading to 33% of the adolescent population considered obese or overweight. Body weight and associated lifestyle behaviors track from childhood to adulthood. Thus, preventing adulthood obesity through early and frequent intervention is essential to decrease the prevalence and severity of chronic diseases and illnesses.

Dental clinics offer an opportunity for obesity prevention through the Healthy Weight Intervention (HWI). The HWI consists of calculating a child’s Body Mass Index (BMI) percentile by age and gender, completing a survey about nutrition and lifestyle habits, then setting goals to improve those habits. While several factors contribute to obesity, more interventions will serve to increase a patient’s awareness of healthy decision-making.

We hypothesized that performing the HWI for children 2.5-6 years old would be easily adapted into clinical practice, as well as show reduced risk promoting behaviors over the 1.5-year observation. To test these hypotheses, 120 out of the 200 expected subjects were recruited. They were assessed for BMI and their parents completed the HWI survey. Survey questions concerned sugary drink, fruit and vegetable consumption, eating patterns, amount of physical activity and TV time, and other behavioral questions. Feedback from clinicians and parents were utilized to enhance the efficacy of intake forms and survey proceedings.

To date, 78.31% of subjects were normal weight (BMI = 5-85th percentile), 15.63% were overweight (BMI>85th percentile), and 6.06% were underweight (BMI<5th percentile). With respect to obesity risk habits, 67.8% watched more than 2 hours of TV per day and 58.3% ate less than 5 servings of the recommended fruits and vegetables per day. These data indicate that a majority of children’s parents reported behaviors that put their children at greater risk for being overweight in the future. In the two follow-up visits at 6 and 12-month intervals, we will examine whether or not there are changes in risk behaviors for obesity and in anthropometrics, using generalized linear mixed models that will fully utilize the longitudinal nature of the data.

We acknowledge the challenges with analyzing HWI in 2.5-6 year old children. Since parents will be answering these surveys on behalf of their children, biases that reflect better parenting strategies may be introduced. Furthermore, using BMI measurements may not capture the most accurate assessment of childhood obesity. However, the HWI survey and procedures were altered through patient, parent and clinician feedback to eliminate biases and improve efficacy.
Lieberman’s Scrollable Seminars in Radiology: An Education Mobile Web App

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The mobile environment is rapidly changing as touch-enabled devices become more ubiquitous. Touch-enabled site navigation provides a simple user interface that can be used for a wide variety of educational needs. Our purpose was to create a dynamic radiologic mobile web app, with advanced features, to enhance the learning experiences of students, trainees, and continuing medical education faculty across many specialties. As a web app, Lieberman’s Scrollable Seminars in Radiology runs on the Internet, so is compatible with mobile devices of many types and brands. This is in contrast to the brand-specific, type-specific apps found on many tablets and phones today.

Lieberman’s Scrollable Seminars in Radiology hosts a series of radiologic cases that interactively display an individual patient presentation. Users are offered quiz questions, at regular intervals, addressing patient workup and radiologic imaging findings to enforce efficacious image ordering and accurate diagnosis. The web app is encoded with “scrollability,” allowing users to scroll through all images within a CT or MRI series to accurately mimic the radiology work environment. This is in contrast to more traditional teaching formats of showing only one static, labeled image. Touch capabilities of mobile devices allow easy movement through series, easy content navigation, and image zooming so subtle findings can be appreciated.

After diagnosing the patient, users are offered a detailed discussion on the disease. The information provided usually includes a definition, epidemiology, risk factors, pathophysiology, clinical presentation, radiologic findings, treatment, and prognosis. Certain diagnoses will have additional information where appropriate on anatomy and embryology. The discussions link to several companion patients demonstrating additional findings typical for the condition in question.

The Seminars are grouped by specialties into Musculoskeletal, Chest, Maxillofacial, Abdomen, Neuroradiology, and Emergency. They are offered by diagnosis or as unknowns so that trainees may assess their own knowledge base. Each section offers comprehensive image libraries for all diagnoses. These too can be displayed with or without labels, again for self-testing. Diagnostic summaries can be downloaded for later review.

In conclusion, radiology at the workstation requires scrolling through many CT or MRI series in full, and key images are visualized in context of the surrounding planes. As a result, digital methods of teaching radiology with scrollability and zoomable function for CT and MRI are optimal. Lieberman’s Scrollable Seminars in Radiology provides a user-friendly, highly detailed, interactive mobile web app for medical students, residents, and faculty across many specialties.
The Content of Early Palliative Care Consultations: A Qualitative Study

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Traditionally, patients receive palliative care (PC) consultations late in the course of illness, in the inpatient setting. Our group at the Massachusetts General Hospital has shown that “early” PC, initiated shortly after the diagnosis of metastatic cancer, leads to better measures of quality of life, fewer depressive symptoms, less aggressive end-of-life (EOL) care, and longer median survival.

We are in the midst of a new randomized controlled trial in which patients recently diagnosed with metastatic lung and non-colorectal gastrointestinal malignancies are randomized to receive either standard oncology care alone or standard oncology care with early PC. In addition to confirming the efficacy of early PC, we aim to identify the key components of early PC that mediate patients’ improved outcomes. In this study, we perform qualitative analysis on transcripts of our subjects’ consultations with PC clinicians.

We first held focus group interviews with PC clinicians on our service to generate a thematic scheme of the components of early PC and the roles of PC clinicians. We are now collecting audio-recordings of all PC consultations with 14 study subjects who have been randomized to receive early PC. Of these consultations, we are transcribing audio-recordings from different points over the course of patients’ illness trajectories: early (often the first consultation), middle, and late (near the EOL). We are coding the transcripts using NVivo 10 qualitative analysis software (QSR International). At least two investigators on our research team are analyzing each transcript.

Our initial results, integrating analyses of the focus group interviews and several early PC consultations, have identified seven domains of early PC: Assessing and Managing Symptoms, Facilitating Advance Care Planning, Advising Decision-Making about Anti-Cancer Treatment, Facilitating Medical Understanding, Supporting Caregivers, Facilitating the Patient’s Coping with Terminal Illness, and Developing and Maintaining the Relationship with the Patient and Caregivers. We are now in the process of analyzing the remaining transcripts. Our results will identify further subcategories within each of the domains, and we will make distinctions between the components of early, middle, and late consultations. Ultimately, we will use our results to create a draft of an early PC manual to inform clinical practice and further research in PC.
Foveal Disorganization of Retinal Inner Layers as Predictor of Visual Acuity in Diabetic Macular Edema

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Ocular complications from diabetes are a major cause of morbidity worldwide and a leading etiology of visual loss in most developed countries. Diabetic macular edema (DME) is a frequent manifestation of diabetic retinopathy and is characterized by leakage of the retinal vasculature into the macula, resulting in retinal edema and reduced vision. The ability to predict future visual acuity (VA) outcomes in patients with DME for both clinical management and research purposes is a major unmet need.

The non-invasive, readily-performed imaging modality of spectral domain optical coherence tomography (SDOCT) is an attractive method for DME assessment given its ability to provide objective, reliable, high-resolution imaging of retinal anatomy and quantification of central retinal thickness. This research aimed to identify SDOCT biomarkers that predict VA in eyes with center-involved DME.

Ninety-six participants (120 eyes) with baseline DME were evaluated. Demographic information, best-corrected VA, and SDOCT images were collected at baseline, 4, and 8 months. A 1mm-wide foveal area was evaluated by SDOCT for extent of disorganization of the retinal inner layers (DRIL), cysts, hyperreflective foci, microaneurysms, cone outer segment tip visibility, and external limiting membrane (ELM) or photoreceptor disruption and reflectivity.

Greater baseline DRIL correlated with worse baseline VA (p<0.0001). DRIL increase over 4 or 8 months was associated with 8 month VA worsening (p<0.0010, <0.0010). A multivariable model including 4 month change in VA, DRIL, and ELM disruption was highly predictive of 8 month VA change (r=0.80). Each ~300µm DRIL increase over 4 months predicted a 1 line VA decline at 8 months. When DRIL decreased ≥250µm at 4 months, no eyes had VA decline of ≥1 line at 8 months, but 78% had VA improvement of ≥1 line. When DRIL increased ≥250µm at 4 months, no eyes had VA improvement ≥1 line at 8 months.

Foveal DRIL is highly associated with VA, and change in DRIL may accurately predict future change in VA. Early change in DRIL identifies eyes with likelihood of subsequent VA improvement or decline. Thus, DRIL may represent a robust, noninvasive biomarker of VA response and facilitate patient counseling, management, and selection for clinical trials.
Functional changes in the trigeminal nucleus of migraineurs - a fMRI study

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Migraine patients typically exhibit abnormal habituation in response to repeated stimuli. This is suspected to be a result of dysfunctional sensory processing within the central nervous system (CNS), which involves both neuronal and vascular structures. Of these regions, the trigeminal nucleus warrants particular attention due to its dual role in receiving and processing sensory information. Previous literature has already demonstrated changes in trigeminal nucleus activity in migraineurs, but the mechanism remains largely unclear.

Thus, we hypothesized that the trigeminal nucleus plays a key role in the abnormal habituation of migraineurs, and that vagal nerve stimulation (VNS) may modulate the region’s activity. We induced habituation in the trigeminal nucleus with repeated somatosensory stimuli delivered to the supraorbital region. VNS, a poorly-understood technique that has been shown to relieve migraine symptoms, was added to explore any further functional changes to the trigeminal nucleus. We utilized a functional MRI method to determine whether the trigeminal nucleus and related brain regions are activated during abnormal habituation. To explore the difference in brain response to repeated somatosensory stimuli in healthy subjects and in those with chronic pain caused by migraines during concurrent vagal nerve stimulation. Subjects will be evaluated in an inter-ictal state (i.e., not during an active attack).

Associated with VNS, we found significant changes in the response of the trigeminal nucleus and of the limbic brain regions (including the amygdala, anterior cingulate cortex, and periaqueductal gray) between experiments with and without VNS in the same subjects. This may provide a novel therapy for migraine patients, who currently lack effective treatments. Given the high (~12%) prevalence of migraine in Western population, our work should find a wide audience in both the scientific community and the general public.
Evaluation of artifacts associated with retinal nerve fiber layer imaging using spectral-domain optical coherence tomography in glaucoma patients

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Glaucoma is the second leading cause of blindness in the world, affecting more than 2.8 million people in the United States alone. It is an optic neuropathy characterized by the death of retinal ganglion cells, the axons of which converge to form the retinal nerve fiber layer (RNFL). As a result, glaucoma causes RNFL thinning. Imaging of the RNFL, therefore, has important clinical value to not only diagnose glaucoma but also follow disease progression.

Optical coherence tomography (OCT) is a noninvasive imaging technique that uses low-coherence interferometry to generate images of any optically accessible tissue. The current commercially available spectral domain OCT (SD-OCT) machines, such as the Spectralis OCT, provides ultrahigh-speed images, with better resolution and sensitivity compared to older time domain OCT (TD-OCT) devices. Although automated SD-OCT measurements allow for quantitative and objective assessments of early RNFL thinning, SD-OCT, or any test, is limited by the quality of the test. Errors either in data acquisition or software analysis may result in erroneous RNFL measurements, which may lead to an inaccurate clinical assessment. It is therefore important for the clinician to recognize when such imaging artifacts or inaccuracies occur.

In order to demonstrate and quantify the prevalence of specific artifacts with Spectralis OCT scanning of RNFL thickness, 1207 adult patients who underwent ophthalmic examination and Spectralis scan were enrolled in the current retrospective study. Twelve different types of artifacts were identified: 1) algorithm failure with anterior RNFL layer misidentification, 2) algorithm failure with posterior RNFL layer misidentification, 3) incomplete segmentation, 4) posterior vitreous detachment (PVD)-associated error, 5) peripapillary atrophy (PPA)-associated artifact, 6) chorioretinal atrophy (CRA)-associated artifact, 7) myelinated nerve fiber layer (MNFL)-associated artifact, 8) de-centration, 9) poor signal, 10) missing parts of scan, 11) cut edge, and 12) motion artifact. Each individual artifact type was described and the incidence of which was quantified.

Additionally, the association of particular types of artifacts with different patient demographic and ophthalmic factors was evaluated. Patients’ age, visual acuity, refractive error, astigmatism, cataract status, stage of glaucoma, visual field reliability, glaucoma diagnosis, and ability to take fundus photograph on the day of the Spectralis scan were identified and recorded from the patients’ electronic medical record when they were available.

The results are still pending. To our knowledge, this is the first study evaluating the prevalence of Spectralis OCT scanning artifacts of RNFL.
Dental Care Spending and Sources in Mexico Before and After Seguro Popular

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The implementation of Seguro Popular (SPS) in Mexico in 2004 aimed to provide previously uninsured populations with coverage for a broad range of medical services, including seven dental services, with the ultimate objective of reducing out-of-pocket (OOP) and catastrophic expenditure on healthcare. However, SPS only finances care provided by public clinics such as those run by the Social Security Administration (SSA) and not that provided by private clinics, where much dental care is sought and provided. It was hypothesized that an increase in SPS-mediated coverage of care provided by public clinics would lead to both decreased out-of-pocket dental expenditure and an increase in care sought at public clinics versus private clinics.

Longitudinal analysis was performed using data from the biennial National Household Income and Expenditure Survey (ENIGH), years 2000-2012, and the National Health and Nutrition Survey (ENSANUT), years 2000, 2006, and 2012. Measurements were made via the ENIGH of changes in out-of-pocket spending and on percentages of households with spending on expenditure codes related to dental care. Preferred source of care before and after SPS implementation were assessed via the ENSANUT healthcare user survey.

Following SPS implementation, the percent of households with out-of-pocket dental spending generally declined, from a 10-year-high of 8.25% in 2000 to 3.12% in 2012. However, the average amount spent by households which did spend did not show significant change; average expenditure by those who did spend was $1,059 in 2000, $1,593 in 2002, and between $1,379 and $1,416 for every year thereafter. Meanwhile, in the years between 2000 and 2012, percent of dental care sought in SPS-accepting clinics increased from 20.00% to 29.61%, while the percent sought at private clinics decreased from 50.35% to 39.32%. On the other hand, healthcare overall sought at SPS-affiliated sites decreased from 35.71% to 28.01% with privately-sought care decreasing more modestly from 25.05% to 22.94%.

In the years following SPS implementation, dental care has increasingly been sought at public clinics, where care is free, instead of at private clinics where care must be financed out-of-pocket. Simultaneously, the percent of households with any out-of-pocket expenditure on dental care decreased during the period in question, but the average amount spent by these households showed no visible trend.
Evaluation of the effect of second opinion radiology interpretations on repeat or additional CT or X-ray imaging for pediatric patients who are transferred to the emergency department (ED) at MGH

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In the United States, approximately 2.2 million patients are transferred to larger, urban tertiary care centers for advanced care after being initially evaluated at regional medical centers and community hospitals. Upon transfer to the larger medical centers for continuity of care, patients are either accompanied by their imaging results or get reimaged on arrival.

When patients are referred with data from prior imaging studies, clinicians may often prefer formal second-opinion consultations of these studies by local radiologists for various reasons including the availability of subspecialty expertise or confirmation of diagnosis. Such consultations are billed to the insurance and become part of the patient’s medical record. In this study, we compare whether local radiologists’ formal interpretations of external CTs accompanying transfer patients lead to less subsequent radiology (CT and MRI) imaging utilization than “curbside” or informal consultations.

We performed a retrospective study of pediatric (ages 0-18) electronic medical records that contained external images (CTs) uploaded between May 2011 and June 2012. Each emergency department (ED) transfer pediatric patient’s medical record was reviewed to determine if a repeat CT or additional MRI imaging was performed. ‘Repeat CT imaging’ was defined as exactly the same type of CT examination performed in our ED within 48 hours of the patient's initial external CT study. ‘Additional MRI’ was classified as subsequent MR imaging of the exact body type as the CT also performed within 48 hours of each other. The institutional review board approved the retrospective review of patient data for this HIPAA-compliant study and waived the need for individual informed consent.

671 outside pediatric CT images were uploaded into our institution’s image repository (PACS) between May 2011 and June 2012. Of these, 196 cases met inclusion criteria of being uploaded within 48 hours of the transfer patient’s admission to our ED. Among them, 64/196 received official second opinion reads and 132/196 received curbside/unofficial reads. A total of 17 repeat CTs and 40 additional MRIs were performed.

Our study found that when there was a curbside read, more MRIs were ordered as additional imaging (24/40) compared to when there was an official second-opinion read (16/40). Curbside reads of external Brain CTs resulted in the most repeat CTs (9/17) and the most additional MRIs (22/40) compared to official reads (4/17 CTs and 11/40 MRIs).

This study suggests that compared to curbside reads of external CTs accompanying patients transferred to our ED, official second-opinion reads reduce the rate at which repeat CTs and additional MRIs are performed.
The Institute of Medicine estimates that 100 million US adults experience chronic pain, costing the nation between $560 and $635 billion dollars per year. Data suggest that the elderly are less frequently treated for pain, and have more underreported pain than does the general population. Furthermore, pharmacologic treatments for pain have limited long-term effectiveness, and carry high risk for older patients, who are often more sensitive to their adverse effects.

Due to the high costs, limited effectiveness, and high risks associated with conventional therapies for the treatment of pain in elderly populations, there is a necessity for non-pharmacologic approaches to pain management. In light of this need, we examined the effectiveness of a pilot program at a community health center that used a multimodal, non-pharmacologic strategy to manage pain in older patients.

From September 2012 until May 2013, the Benson Henry Institute’s Wellness Center at MGH Revere HealthCare Center offered the Moving With Ease program, which provided low-cost, non-pharmacologic treatments for chronic pain, including massage, acupuncture, yoga, and relaxation training, to 25 patients over the age of 50. Primary health outcomes were pain and quality of life, as measured by the Brief Pain Inventory (BPI), the Patient Health Questionnaire (PHQ-2), and the Perceived Stress Scale (PSS). We analyzed the difference between pre- and post-program scores using paired t-tests with P<0.05. In addition, we conducted semi-structured interviews to further examine participant experiences. We are in the process of evaluating these interviews using qualitative coding software.

We collected data from all 25 patients; of this group, we interviewed 10 participants about their experiences with the Moving With Ease program. Participant ages ranged from 52 to 88 years, with a mean age of 70 years; 16 of the 25 participants were women. We observed improvements in some scores but did not find statistically significant improvements between participants’ pre- and post-program scores on the BPI, PHQ-2, or PSS. A preliminary analysis of the qualitative data suggests that patients’ perceived benefits from participating in the program are notable, and in several cases, life-changing. We expect that further analysis of the qualitative data will provide insights into the nature of this apparent discrepancy between our quantitative and qualitative findings.

Limitations of our approach include its small sample size and possible response bias, since not all participants were available to be interviewed.
Rural urban differences in Obesity and Body Image in Ghana

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The growing incidence of non-communicable diseases (NCDs), many of which are strongly associated with overweight and obesity, coinciding with the burden of infectious disease in middle and low income countries poses a significant threat to recent gains in morbidity and mortality.

NCDs like diabetes and coronary artery disease accounted for 28% of deaths in Africa in 2004; a figure expected to rise to 27% over the next decade.

Ghana is no exception; the number of overweight and obese women nearly doubled between 1987 and 2007. Another study revealed that 50% of women surveyed in Accra, the nation’s capital, were overweight or obese and favored a slightly overweight build as an ideal body image. While traditional values have been enough to explain these rates in the past, rising levels of obesity beyond such ideals could signal a troubling public health concern.

Understanding individual perspectives and identifying socio-cultural forces that influence such ideals could help identify at risk populations and shape public health interventions.

In recent decades profound changes have altered traditional Ghanaian culture, impacting a wide range of issues from societal values to nutritional choices. We sought to identify how one aspect of modernization – rural-urban migration—has affected body image.

We hypothesized that urban dwellers will have greater body dissatisfaction scores (discordance between ideal and actual body images) and higher rates of obesity relative to rural dwellers.

A verbally administered survey and basic physical measurements were used to collect data from 332 adults (>18 years) who presented at a district hospital in rural Ghana. This included 149 female and 183 males, 159 rural dwellers, 22 urban dwellers and 151 semi-urban dwellers. The BMI distribution among our population appears markedly different from that of the predominantly urban population obtained by our research team last summer (<18.5: 4.82%; 18.5-24.99: 70.18%; 25-59.99: 17.77%; >30: 7.23%). The mean CBI was 14.320 and the mean IBI was 14.338 giving our population a mean discordance of -0.981.

This preliminary analysis appears to support our hypothesis but more detailed regression analysis and frequency distributions to identify trends according to demographic assessment areas and other variables will be conducted. The data will then be compared previous data collected by our research team in urban Cape Coast to determine differences between the populations.
Understanding the Etiology of Pediatric Hydrocephalus in the Developing World

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Hydrocephalus is the most common neurosurgical disorder in children; epidemiological data on its prevalence is only available for developed countries, where it affects 3-5 live births per 1000. In the developing world, it is estimated that an even higher number of infants are affected. The high prevalence in the developing world is especially problematic considering the maldistribution of neurosurgeons, with approximately a third of the world’s population covered by only a twentieth of its neurosurgeons.

An important step in addressing this unmet need is a thorough understanding of the etiology of disease. Hydrocephalus can occur in children through a diverse set of etiologies, which are broadly categorized into congenital and acquired etiologies. Recent studies in Uganda found that 60% of infant hydrocephalus cases were secondary to neonatal infection. This represents a very different picture from the US, where the vast majority of pediatric hydrocephalus is congenital in nature. It is hypothesized, but not yet demonstrated, that this post-infectious hydrocephalus (PIH) makes up the majority of cases in other countries across Sub-Saharan Africa and the developing world. We aimed to determine the incidence of PIH among infants with hydrocephalus presenting to sites in Zambia, Tanzania, Malawi and Nigeria.

Initially, data was collected through an existing database, set up through CURE Hydrocephalus, an international organization working to improve care to children with Hydrocephalus in the developing world. This summer, Dr. Warf and I worked remotely with surgeons and Clinical Care Coordinators in order to train them to accurately populate the database. The data provided initial support to the hypothesis that the majority of cases in these countries would also be post-infectious, but Dr. Warf and I determined that additional information was necessary in order to substantiate these findings. Entries often contained the surgeon’s diagnosis, without enough ancillary data for confirmation. In a new trial, we sought to provide verifiable data points, and avoid incomplete and inconsistent entries for patients. Working with Dr. Warf, I designed an original form for the surgeons and care coordinators to complete in order to accurately provide verifiable information on the etiology of hydrocephalus, while minimizing the time required to enter data at the sites. We are currently in the process of beginning a new 6-month collection period.
Assessing surgical margins in breast cancer specimens: 2D mammography vs. 3D tomosynthesis

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For patients diagnosed with breast cancer, surgeons often perform lumpectomy to remove the malignancy along with a rim of normal tissue (surgical margin). Imaging of the excised tissue during surgery permits the radiologist to assess margin status and guide the surgeon accordingly. Subsequently, the pathologist examines the specimen margins microscopically. If final pathology indicates positive or close margins, additional surgery is usually necessary.

Tomosynthesis is a new 3D breast imaging modality that may provide better margin assessment of excised specimens over conventional 2D mammography. Improved margin assessment at the time of surgery could reduce re-excision rates. The aim of this study was to determine whether 3D tomosynthesis is better than 2D mammography for radiographic margin assessment. We hypothesized that specimen tomosynthesis permits more accurate margin evaluation. We also investigated whether acquiring 2 oriented orthogonal views of a specimen improves margin assessment over the conventional one-view non-oriented approach.

100 surgical specimens will be imaged using 3 imaging protocols: conventional unoriented 2D image, 2 oriented 2D images, and 2 oriented 3D images. 2D images are acquired on a dedicated specimen unit and 3D tomosynthesis images on a Hologic unit. As of 9/10/2013, 31 specimen studies were reviewed by 3 board-certified breast imagers. Image sets were read in random order to determine margin status on imaging. Surgical pathology was the gold standard for margin status.

Of 31 cases, 13 were excluded given benign pathology leaving 18 cases, of which 8 had positive margins (< 1mm), 9 had close margins ( > 1mm but < 5mm), and 1 had negative margins (> 5mm). The readers accurately predicted margin status 36.1% using 2 oriented 3D images, 22.2% using 2 oriented 2D images, and 11.1% using single unoriented 2D image. Positive margins were accurately predicted 43.8%, 12.5% and 12.5% of the time, respectively. There was substantial inter-reader variability with regard to margin status. Following study completion we intend to analyze data using McNemar test. Limitations include: variation in specimen orientation; lack of compression for 2D and use of light compression with 3D imaging; and lack of magnification of large specimens due to limited detector plate size of dedicated specimen unit.

Although data continues to be collected, preliminary review of 18 cases suggests that 3D tomosynthesis appears to better assess surgical margins than conventional imaging and that 2 oriented orthogonal images permit better margin assessment than a single unoriented image.
Racial/Ethnic Differences in Parents’ Perceptions of Family-Centered Care during Pediatric Hospitalizations

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Family-centered care (FCC) establishes a partnership between providers and a family to provide care that respects the family’s values and preferences. It is associated with better clinical outcomes and higher patient satisfaction. Studies of outpatient care have shown that non-White parents are less likely to report receiving FCC; however, it is unknown whether these differences are also present in the inpatient setting. The aim of the study was to determine whether parent report of FCC during pediatric hospitalizations differs by race/ethnicity.

We completed bivariate and multivariate analyses of 1,268 surveys from the pilot test of Pediatric HCAHPS, a survey administered between July and October 2012 to parents of recently hospitalized children. The four outcome variables were three items measuring aspects of FCC and one overall rating of the hospital stay. The primary independent variable was child’s race/ethnicity (Asian/Pacific Islander, Black/non-Hispanic, Hispanic, White/non-Hispanic). Covariates included parent’s preferred language and education level, child’s age and health status, and means of admission (born during hospitalization, ER admission, other).

Most parents reported receiving high levels of FCC and rated their hospital stay highly. Specifically, 80.5% said providers always kept them informed about what was being done for their child, 78.8% said providers always involved them in discussions as much as they wanted, 81.6% said that doctors always listened carefully to them, and 80.7% of parents rated their hospital stay a 9 or 10 on a ten-point scale. Compared with White parents, Black parents had higher odds of reporting that providers always kept them informed (OR 2.0, p<0.05) and that doctors listened carefully (OR 2.1, p<0.05), whereas Asian/Pacific Islander parents had lower odds of rating the hospital stay highly (OR 0.6, p<0.05) and reporting that providers always involved them in discussions (OR 0.6, p<0.05). In multivariate analyses, these differences were no longer statistically significant, with the exception that Hispanic (aOR 1.8, p<0.05) and Black parents (aOR 2.2, p<0.05) had higher odds than White parents of reporting that providers always kept them informed.

Most racial/ethnic differences in parent report of FCC and overall hospital rating diminished after controlling for sociodemographic factors, child health status, and means of admission. Even after adjustment, however, Black and Hispanic parents had higher odds of reporting that providers always kept them informed. Limitations of this study included non-response bias and restriction to eight participating hospitals. The forthcoming analysis of a larger, more nationally representative dataset (n=~15,000) will provide more generalizable findings.
Effect of Short Term Fructose and Dextrose consumption Hepatic Metabolism

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Diets high in fructose and sucrose may increase the risk of obesity and non-alcoholic fatty liver disease. Fibroblast Growth Factor 21 (FGF21) has complex metabolic actions, including regulation of hepatic fatty acid oxidation and browning of white adipose tissue. Previous data indicated that the induction of FGF21 expression by Carbohydrate Response Element Binding Protein-β (ChREBP-β) plays a key role in long-term adaptation to diets high in sugars. However, the role of FGF21 and ChREBP-β in acute adaptation to feeding high sugar diets is unknown. More insight into the hepatic metabolism of dextrose and fructose, may provide essential insight into obesity-related metabolism and suggest possible therapeutic targets.

Our aim was to define the short-term adaptive processes induced by high fructose (HF) and high dextrose (HD) diets, expecting that each would cause distinct changes in hepatic metabolism. We fed mice chow (C), HD (60%), or HF (60%) diets for 48 hours. The mice were euthanized, their liver enzyme expression was analyzed using Q-PCR, and their serum FGF21 levels were measured.

Compared to C (Set to 1) and HD mice, HF mice showed increased expression of several hepatic enzymes involved in fructose metabolism, including FGF21 (HF-1.65, HD-1.17), ChREBP-β (HF-8.26, HD-2.6), Liver Pyruvate Kinase (HF-5.78, HD-1.39), Fatty Acid Synthase (HF-12.29, HD-3.21), and Stearoyl-CoA desaturase (HF-6.46, HD-2.11). In both the HF and HD mice, serum FGF21 levels were proportionally far greater than FGF21 expression in the liver (C-197.13 pg/ml, HF-734.94 pg/ml, HD-1262.16 pg/ml).

This data confirms that ChREBP-β expression in the liver increases after short-term consumption of high sugar diets. Furthermore, for the first time, we showed that short-term consumption of these diets leads to induction of liver FGF21 expression. The gene induction pattern in the acutely HF fed mice, was similar to the gene induction pattern previously observed in chronically HF fed mice. In the chronically HF fed mice, this pattern correlated with metabolic disregulation. Our data may be an indicator of early metabolic disregulation in the HF fed mice. Higher serum FGF21 in the HD mice may reflect a non-hepatic source (adipose, pancreas) of FGF21, or may reflect differences in clearance.

This data confirms that short term exposure to diets can be used to analyze the hepatic effects on fructose and dextrose metabolism. Furthermore, for the first time we describe a novel regulatory pathway for of the induction of FGF21.
Dental pulp-like tissue regeneration by PTEN inhibition

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The goal of this study is to introduce a novel cell homing cocktail for dental pulp regeneration in endodontically treated teeth. Currently, root canal therapy is the treatment of choice for teeth with compromised dental pulp. Although the procedure has its advantages, it also leaves the tooth devitalized and brittle, making it more prone to fractures. A number of studies report dental pulp-like tissue regeneration using dental pulp stem cells. Dental pulp stem cell transplantation, however, is costly, with cell harvesting and shipping. Furthermore, a healthy tooth will have to be sacrificed if wisdom teeth are not an option. Thus, dental pulp regeneration by chemotaxis-induced cell homing is a more attractive method, and has been previously demonstrated using a cocktail of various growth factors. In my study, phosphatase and tensin homolog deleted on chromosome 10 (PTEN) inhibitor is used to speed up and enhance the pulp regeneration process. PTEN inhibition has been linked to angiogenesis, accelerated wound healing by promoting cell migration, and adult peripheral nerve outgrowth. With these effects of PTEN inhibition, I hope to create a more efficient means of dental pulp regeneration that will bring us closer to clinical translation.

Since this is a new, self-designed project, this summer was used to establish new protocols and to probe the effect of PTEN inhibition on dental pulp reinnervation. Since the tooth is targeted for innervation by sensory nerves from the trigeminal ganglion (TG), a TG explant protocol was created to observe the effect of PTEN inhibition on TG outgrowth. The mouse TG explants were incubated with or without a pharmacological PTEN inhibitor. Two PTEN inhibitors were tested for reproducibility. As shown by contrast imaging and immunofluorescence staining, the treated TG explants consistently showed denser neurite outgrowth than the untreated TG explants. This suggests the possibility of using PTEN inhibition for tooth reinnervation. For this reason, the focus of the project was redirected from investigating the developmental role of PTEN in tooth innervation to its clinical potential in dental pulp regeneration. With these initial results from *in vitro* studies, I plan to do a third explant trial to demonstrate reproducibility, and to eventually perform *in vivo* experiments. The *in vivo* experiments will involve the subcutaneous implantation of an extracted, endodontically treated tooth loaded with gel consisting of PTEN inhibitor and other growth factors, and histological analysis to look for revascularization and reinnervation in the implanted tooth.
Physiologic investigation of insulin resistance, visceral fat accumulation, and the renin-angiotensin-aldosterone system in HIV-infected patients

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Compared to the non-infected population, HIV-infected patients are at increased risk for visceral adipose tissue (VAT) accumulation, insulin resistance (IR), and cardiovascular disease (CVD). Accumulating evidence suggests that activation of the renin-angiotensin-aldosterone system (RAAS) promotes adipose tissue dysfunction and cardiometabolic abnormalities in HIV infection.

In addition to its role in regulating blood pressure, RAAS engages in complex crosstalk with adipose tissue. This crosstalk results in excess aldosterone signaling, which may contribute to the development of IR and CVD. Previous research has shown that 24-hour urine aldosterone secretion is increased in HIV-infected women compared to non-infected age- and BMI-matched controls and is positively associated with VAT accumulation and HbA1c.

Based on this data, we hypothesized that autonomous activation of RAAS contributes to IR in the HIV-infected population, with excess VAT further exacerbating this relationship. To test this hypothesis, 21 normotensive, non-diabetic, HIV-infected men and women were evaluated at baseline for RAAS activity, glucose homeostasis, and VAT accumulation, assessed via serum aldosterone (SA), HOMA-IR, and MRI, respectively. Measurements of SA and HOMA-IR were then repeated after a 7-day low-salt diet to acutely stimulate RAAS.

At baseline, HIV-infected individuals with excess VAT demonstrated significantly higher HOMA-IR compared to those without excess VAT (1.6 [0.9, 2.7] vs. 0.6 [0.5, 1.0]; p = 0.02). There were no significant differences in blood pressure, 24-hour urine sodium, or plasma renin activity between the groups.

Compared to baseline measurements, the low-salt diet resulted in significantly increased SA (4 [3, 9] vs. 15 [10, 32] ng/dl; p = 0.001) and HOMA-IR (1.0 [0.6, 1.9] vs. 1.8 [0.9, 2.7]; p = 0.009). After the low-salt diet, SA (p = 0.01) and VAT (p = 0.001) were significantly, independently, and positively associated with HOMA-IR, with a two-way interaction term (p < 0.0001). The relative median increases in SA and HOMA-IR after the low-salt diet were higher among subjects with excess VAT compared to those without excess VAT.

These data suggest that RAAS activation may contribute to IR in the HIV-infected population, particularly in those with excess VAT. Planned future studies comparing these results to non-HIV-infected control patients and assessing RAAS activation under high-salt conditions will elucidate the degree to which RAAS activation is autonomous and contributes to IR in HIV. These studies provide novel insight into the relationship between RAAS activation, glucose homeostasis, and visceral adiposity in HIV-infected patients.
Assessing the Information on Post-Treatment Breast Cancer Survivors and Exploring Survivorship Care in Mexico

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While much focus and attention in global health has historically been placed on the treatment and prevention of communicable diseases, recent efforts have begun to raise awareness of the need to allocate attention to non-communicable and chronic diseases as well, and more specifically, cancer—currently one of the leading causes of mortality in low- and middle-income countries (LMICs). Cancer forms a very complex component of the global burden of disease not only because it presents in different forms, each having its own unique health complications, but also because addressing the disease can consist of three different phases. These include detection, treatment, and post-treatment survivorship care.

This project aimed to develop a framework for the needs of Latin-American post-treatment breast cancer survivors through an extensive literature review and subsequently assess the representation of these needs in three Mexican national databases. Because breast cancer survivorship has only recently come to light as an issue—as a result of improved treatment and access to care—we predicted that there would be very little information in the databases on post-treatment breast cancer survivors and their health care needs.

Three major databases were explored: the National Institute of Cancer hospital records on breast cancer patients, the National Survey of Health and Nutrition from the year 2012, and the Sistema de Información de Cáncer en la Mujer (SICAM). In addition, an extensive amount of time was spent at the Instituto Nacional de Cancerología in an effort to understand the experience of a breast cancer survivor in a tertiary cancer care setting in Mexico. As expected, very few variables were found within the databases pertaining specifically to breast cancer survivorship care, and among the challenges faced by breast cancer patients seen in a public tertiary cancer center were long waiting times, little patient awareness of survivorship services and the absence of guidance for patients after having received treatment.

The fragmentation of the Mexican health care system among private and public sectors, as well as the lack of a Mexican national cancer registry, made it very difficult to find reliable, consolidated data on large numbers of breast cancer survivors. In addition, there was scant literature on the survivorship needs specific to Latin American breast cancer survivors. While there are currently two studies underway aiming to bring light to the needs of Mexican breast cancer survivors, there still lacks a comprehensive, concise Mexican cancer survivorship database.
Promoting Health for Domestic Workers and Their Clients: A Collaborative Needs Assessment

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Domestic workers comprise one of most underpaid, unprotected, and unstable employment sectors in the U.S. today. National surveys highlight significant health risks faced by this population including stress and injuries. However, there is little data available about the specific health needs of domestic workers in the greater Boston area.

This pilot needs assessment seeks to address the knowledge gap by engaging domestic workers (including home care workers, nannies, and housecleaners) in focus groups to discuss their experiences with employment and health. The project takes a participatory approach by partnering with a local community-based organization of domestic workers and incorporating training and collaboration throughout the process.

First, key informant interviews were conducted with domestic worker leaders to define the major topic areas of study: working conditions, health and wellness, worker skills and assets, and knowledge of current labor rights. Focus group guides were developed and revised with feedback from key informants. Participants were then recruited through a combination of on-the-street outreach and phone calls to members of the partner organizations. Two domestic worker focus groups were held in community-based settings convenient to the participants. All participants provided full consent and received nominal compensation for their time. Sessions were audio-recorded and documented in standardized notes.

Qualitative analysis identified job “creep” (when an employee is expected to perform more tasks than originally stated), lack of a contract, and perceived poor treatment by the employer as major themes defining many workers’ experiences. The main health concerns identified were stress (both mental and physical), injuries, and back pain. Workers highlighted their love of caring for others as a major asset they bring to their jobs. The majority had been unaware of their current rights under Massachusetts labor laws.

These findings suggest that domestic workers in Massachusetts face challenges to their health that are similar to those experienced by workers in this field in other parts of the U.S. There is a need for improved workplace protections and outreach to domestic workers in the Commonwealth to improve their health and well-being.
Representative characteristics and congressional voting on federal expansions of health care access: a quantitative analysis

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Access to medical care is a fundamental problem in the United States, but few studies have assessed the historical politics of enacting health care reform. In this quantitative analysis, we examined congressional votes on legislation that 1) had a primary focus on broadening access to medical care at a federal level, 2) reached the point of a roll call, and 3) occurred after 1950.

Fourteen bills that fit these criteria were selected from health care reform timelines in popular media. The sample included roll calls on passage, recommittal and major amendments, totaling 12,595 member-specific votes in the House of Representatives and 1,782 member-specific votes in the Senate. We used multiple logistic regression to analyze these votes against 6 representative characteristics: party (Democrat=1, Republican=0), terms served in Congress (TRM), committee membership relevant to the bill (COM), elderly constituent percentage (ELD), constituent median family income (MFI), and constituent Democrat voting percentage in the prior presidential election (DP). Party of the bill sponsor (SPONS) was also included. Constituency demographics were standardized to account for changes over time, and regressions were clustered to control for representative voting across bills.

Legislation was generally introduced under Democratic control, with regards to sponsorship (12/14), House majorities (11/14) and Senate majorities (12/14). Only 1 bill was considered during split party control of Congress. House Democrats voted for these bills 76% of the time, compared to 56% for House Republicans. Senate Democrats did so 82% of the time versus 65% for Senate Republicans.

In the pooled House regression (pseudo-$R^2=0.39$), party (Democratic bill sponsor $1.92\pm0.10$; Republican bill sponsor $-4.03\pm0.19$), COM ($-0.44\pm0.075$), ELD ($0.43\pm0.16$), MFI ($0.45\pm0.18$), DP (Dem. sponsor $9.90\pm0.58$; Rep. sponsor $3.37\pm0.58$) and SPONS ($-9.31\pm0.41$) were significantly associated with voting behavior ($p<0.02$). For the pooled Senate regression (pseudo-$R^2=0.16$), party (Dem. sponsor $1.40\pm0.17$; Rep. sponsor $-0.98\pm0.29$), ELD ($1.09\pm0.46$), MFI ($2.08\pm0.58$), DP (Dem. sponsor $8.24\pm1.74$; Rep. sponsor $-7.59\pm1.21$) and SPONS ($-7.59\pm1.21$) were significantly associated with voting behavior ($p<0.05$). TRM was not significant in either model. Individual bill regressions varied along these findings, consistent with legislative differences to the reforms. No variable collinearities were greater than 0.25.

These results indicate that representative voting on federal expansions of health care access strongly associates with party identification and multiple constituency demographics, particularly voter partisanship. When formulating future health care reforms, policymakers may want to consider these factors and their application to the legislative environment. The observational limits to this study suggest further research is warranted.
Evaluation of school-based health education in raising awareness of Schistosomiasis among children living in sub-Saharan peri-urban slum communities

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The peri-urban slums of Lusaka, Zambia, like many unplanned squatter compounds in developing nations, lack adequate water sanitation and waste management services. Consequently, these slums have been found to harbor significant vulnerability to infection by Schistosoma haematobium. Children are particularly susceptible to infection as they are more likely to bathe, play, and swim in contaminated water. While high rates of schistosomiasis have been found among Lusakan children, there exists a discrepancy between the development of symptomatic manifestations and the recognition of the symptoms as a disease that warrants treatment.

Based on this insight, we hypothesized that in order to address the burden of schistosomiasis experienced by the children of Lusaka, it would be most effective to concentrate on increasing general awareness and promoting widespread prevention. We further conjectured that the development of school-based health education would provide a structured, sustainable format through which such awareness and prevention could be achieved despite limited resource availability.

To evaluate our hypothesis, we partnered with six community schools sponsored by the non-profit organization Communities without Borders. In conjunction with a Zambian health promotion training team, we invited the teachers of these six community schools to participate in health workshops focused around the topics of water sanitation, waste management, and schistosomiasis. Equipped with the appropriate knowledge, these teachers were then asked to design and implement lesson plans for their classrooms.

Baseline and post-intervention data assessing knowledge of water sanitation, waste management, and schistosomiasis was collected on over 300 students. Qualitative observation revealed an increased familiarity with schistosomiasis, with some children capable of independently explaining the parasite’s life cycle. In terms of quantitative analysis, we will evaluate the data obtained as a whole, representing the six schools as a unit, and based on several stratifications: age of the child, specific school attended, and teacher performance at the health workshops.

We believe the quantitative data will enhance our qualitative observations that teachers in resource poor settings have significant potential to spread health knowledge to their students, thereby achieving enhanced awareness and promoting prevention. Nevertheless, we recognize the limitations of our work: language barriers, short intervals between teacher workshops and student assessments, and varying levels of teacher engagement. We hope that ongoing surveillance of schistosomiasis prevalence and student knowledge will offset some of these limitations and further support the efficacy of a school-based health education program in decreasing the rates of parasitic diseases that burden children in developing nations.
Craniopharyngioma and Hypothalamic Obesity: An Exploratory Study

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Craniopharyngioma (CP) is the most common suprasellar tumor of nonglial origin in the pediatric population, and most commonly arises in childhood or adolescence. Hypothalamic damage is a major cause of morbidity in survivors of CP, which causes problems with sleep latency, fatigue, and depression. In patients with CP, hypothalamic damage is strongly associated with hypothalamic obesity (HO). After tumor resection, approximately half of patients develop hypothalamic obesity that is resistant to treatment.

We are conducting a prospective exploratory study into the underlying pathophysiology of HO in CP by comparing CP patients post tumor resection with HO (CPHO) to those CP patients without HO (CPNO) post tumor resection. To do this, during patients’ standard of care clinical visits, they are asked to consent to provide a fasting blood sample to use for proteomics and targeted metabolic profiling, in addition to a chart review. The proteomics analysis will offer an unbiased look into the underlying biological markers of HO, while the chart review will offer information regarding the location, treatment, lab data and clinical information throughout the course of each person’s illness. The metabolic profiling will provide a more targeted look at metabolic markers of HO in CP. Due to changes made to the protocol including adding fasting and pre-visit phone calls, IRB approval has been delayed. Thus, no data has been collected at this time.

The predominant limitation of this study is the small sample size. Due to the rarity of CP, a sample size of ten (five per group) is expected. This small sample size makes it more difficult to detect differences between the two groups of the metabolic profiling and proteomic analysis. Further, due to the high number of tests that will be run on the blood samples, there is a high rate of Type I Error. That said, the analyses will control for alpha error and have the ultimate goal is an exploratory look into potential metabolic and proteomic markers of HO in CP.
The impact of sustained attention training on aspects of sleep in returning veterans

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A large percent of returning veterans from Iraq and Afghanistan have been exposed to combat related stress or traumatic events. As a result, nearly 1/3 of these individuals have a mental health condition such as post-traumatic stress disorder (PTSD), depression, or a traumatic brain injury (TBI). Both sleep disruptions and attention impairments are linked to PTSD and TBI and adversely affect the daily lives of these individuals.

A study recently investigated whether sustained attention training can improve some symptoms related to PTSD and TBI, such as attention, inhibitory control, and sleep. This project followed returning veterans who took part in the sustained attention training program and monitored the effects on their sleep patterns. We hypothesized that sustained attention training would improve the subjects’ quality and quantity of sleep. To test this hypothesis, participants’ (n=54) sleep was measured at home using actigraphy, a commercially available personal EEG, a sleep diary, and a global measure of sleep quality (Pittsburgh Sleep Quality Index, PSQI).

The actigraphy, EEG, diary, and PSQI data were combined into a single data set for comparison. The sleep data was then combined with the attention training database for comparison. Exploratory analyses were performed to confirm the validity of the actigraphy, EEG, and diary as sleep measures. The PSQI is a well-validated measure of sleep and was used in the attention study as a baseline measure of sleep quality. There is a known, repeatable, strong correlation between PTSD and sleep quality. On preliminary analysis, the PSQI was highly correlated with PTSD, as was expected. However, the more detailed actigraphy, EEG, and diary measures failed to correlate with the PSQI or PTSD. As these measures were not able to accurately capture the quality of the participants’ sleep, they could not be used to determine if their sleep quality was affected by the attention training program. That said, we did find that sustained attention training was associated with a trend towards improvement in sleep quality on the PSQI, suggesting that training may have had a positive impact on sleep.

Other studies have found that the reliability of actigraphy and at-home EEG measures are substantially reduced in populations with sleep impairments and our results appear to support this finding for this population. The ineffectiveness of these instruments in populations with poor sleep may be due to gaps in software capability or to a low signal-to-noise ratio.
Dental Care for Special Needs Individuals Attending a Summer Camp in Trinidad and Tobago

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The Republic of Trinidad and Tobago (TT) has one of the highest per capita incomes in Latin American and the Caribbean. This has supported free walk-in health care, including oral health care, in community healthcare facilities. Oral hygiene conditions and education are, nonetheless, not optimal. Non-fluoridated water results in fluoride levels below the optimum range for caries prevention. A majority of primary schoolchildren need some type of treatment (fillings, sealants).

In TT, there is limited awareness of disabilities, especially learning disorders, and no legislation for the systematic provision of special needs education. Special education programs exist due to the efforts of groups/individuals in the private sector. In the US, studies indicate that this population is neglected by dental professionals for various reasons. In TT, some (difficult to access) special needs dentistry is provided at select health centers. Additional data are not available.

The goal of this project was to assess oral health care practices in TT with specific reference to the needs of special needs individuals. A research study and educational module were conducted in collaboration with the annual therapeutic summer camp of the Immortelle Centre for Children with Special Needs (ICC). The campers have moderate to severe special needs in the context of a range of neurodevelopmental disorders; all are of limited intellectual and behavioral competence.

The research study involved surveys and semi-structured interviews of dentists (#19) and campers’ caregivers (#11). Surveys of camp staff (#18) were also conducted. Surveys of these three groups gave different perspectives on the main needs/barriers for dental care. Interviews provided more in-depth understanding of special needs dental clinics, the history and changes in dentistry, and expectations for future special needs dental care in TT.

During the two-week educational module, basic oral hygiene was taught to individual campers. Various teaching strategies (verbal instruction, visual demonstration, props, hand-over-hand instruction) were used and analyzed with the goal of drafting an oral-hygiene curriculum for ongoing use in the ICC. Successful strategies elicited a high class-participation rate and independent action by the camper.

This pilot study found that there is some dental care for special needs individuals in TT, but that this is limited and difficult to access; main needs and barriers to care were identified by providers and consumers. The educational module was implemented successfully; recommendations for integration into the yearly ICC curriculum will be submitted to the director.
Database Construction and Data Analysis as a Quality Improvement Project for the Department of Palliative Care at the Ho Chi Minh City Cancer Hospital

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Pain, other physical and psychological symptoms, and social distress are common among patients with advanced life-threatening illnesses such as cancer. Palliative care provides relief from pain and other forms of distress and is widely considered to be a basic human right. Yet in low and middle income countries (LMICs), pain relief and palliative care are almost always inadequate or unavailable. In Vietnam, which has by conservative estimation at least 70,000 cancer deaths and 150,000 new cancer cases per year, 70% at advanced stage available data indicates that pain is highly prevalent among cancer patients yet rarely well treated.

In response to this unnecessary suffering, Vietnam’s Ministry of Health (MoH) launched a palliative care initiative in 2005 with support from the US President’s Emergency Plan for AIDS Relief and technical assistance primarily from the Harvard Medical School Center for Palliative Care.

As part of this initiative, the Ho Chi Minh City Cancer Hospital, the oncology referral center for all of southern Vietnam, established a Department of Palliative Care in 2008 consisting of an inpatient ward and outpatient clinic. In September 2011, it began providing home care for patients discharged from the hospital with end-stage disease. Previously, such patients had been discharged home with no follow-up.

Patients who are attended to by the home care team are administered the translated African Palliative Outcomes Scale (POS). The scale assesses physical, psychosocial, spiritual, and caregiver distress utilizing a five-point scale. We compared the responses of 81 patients who had answered the POS upon first visit and then upon follow-up with the home care team. Utilizing the Wilcoxon Signed Rank Test, significant differences between initial and follow-up visits were assessed. A cumulative score for patients and caregivers were calculated to interpret the quality of life and level of distress experienced. The average among patients for each question, as well as degree of change between first and follow-up visit will also be analyzed. Finally, patient demographics (including socioeconomics, insurance status, and cancer diagnosis and stage) were gathered and analyzed, in order to conduct multi-variable analysis. Data has been inputted, but final analysis and interpretation are still in progress.

In summary, a patient database was created from the existing patient files at the HCMCCH and patient responses to a POS survey were utilized to interpret the effect of palliative care on the patient’s quality of life. The hypothesis is that treatment from the home care team alleviates distress in end-stage cancer patients.
Sideroflexin 4 Deficiency Results In An Erythroid Differentiation Defect

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Megaloblastic anemia characterizes molecularly heterogeneous disorders, most commonly marked by macrocytosis, red blood cell enlargement, and abnormal nuclear maturation. Aside from vitamin B\textsubscript{12} and folate deficiencies, genetic defects may be responsible for hereditary forms of megaloblastic anemia, though some remain unknown (Ghersim C, et al. 2013 J. Biol. Chem.). Loss of function of the gene Sideroflexin-4 (SFXN4) has been implicated as a cause for combined macrocytic anemia and mitochondriopathy. We have previously shown a defect in SFXN4 in humans and successfully modeled the erythroid and mitochondrial defects in the zebrafish (Hildick-Smith GJ, et al. 2013 AJHG). Here, we expand on prior studies involving SFXN4 in zebrafish and human fibroblasts by generating a murine cultured cell model deficient in SFXN4.

Clustered regularly interspaced short palindromic repeats (CRISPR)-cas targeting technology (Cong L, et al. 2013 Science) was utilized to generate SFXN4 knockout Friend mouse erythroid leukemia (MEL) clones. We conducted a screen of clones using qRT-PCR to select MEL clones with the lowest expression of Sfxn4 mRNA. The CRISPR knockout clone shows significantly reduced Sfxn4 mRNA relative to wild type. Furthermore, the CRISPR knockout's reduced Sfxn4 mRNA is comparable to Sfxn4 mRNA levels in clones silenced by shRNA hairpin constructs.

We also investigated the differentiation and maturation potential of the CRISPR-derived SFXN4 knockout clone. Initially, the MEL clone was differentiated for 3-5 days with DMSO treatment. o-dianisidine stains revealed that the CRISPR knockout clone had a reduction in hemoglobinization. Furthermore, Wright-Giemsa staining demonstrated that the same clone possessed megaloblastic features with immature maturation and a high nuclear to cytoplasmic ratio. Both sets of results from experiments support the hypothesis for an essential role of SFXN4 in vertebrate red cell development.

In summary, our data: (1) supports the hypothesis of SFXN4’s involvement in erythropoiesis and candidacy as a gene for combined macrocytic anemia and mitochondriopathy, and (2) demonstrates the promise of shRNA knockdown and now CRISPR SFXN4 knockout clones as tools for further studying the biochemical relationship between SFXN4 and megaloblastic anemia.
Investigation of the role of c-Myc in development of drug resistance in HER2-positive breast cancer using a novel genetically engineered mouse (GEM) model

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HER2-positive breast cancer, characterized by amplification of Human Epidermal Growth Factor Receptor-2 (HER2), constitutes approximately 12-20% of human breast cancers. The development of resistance to effective HER2 targeted therapies such as Trastuzumab (monoclonal antibody) and Lapatinib (tyrosine kinase inhibitor) is a major problem. Preliminary studies in our lab reveal rapid increases in tumor c-Myc levels following down regulation of HER2 over-expression. C-Myc is a well-known human oncogene, and downstream target of the PI3K/mTOR pathway. It has been implicated in mediating resistance to the PI3K/mTOR inhibitor (BEZ235) in Human Mammary Epithelial Cells\(^2\), but its potential role in mediating recurrence of HER2-positive breast cancer and resistance to anti-HER2 therapies has not been studied.

The purposes of this study were 1.) to characterize the responsiveness of tumors in a novel mouse model of HER2-driven mammary carcinoma to HER2 targeted therapies. 2.) to confirm our initial observation of increasing c-Myc levels as HER2-signaling is blocked in HER2-positive tumor cells 3.) to determine if increased c-Myc levels within HER2-positive tumor cells mediate resistance to HER2 targeted therapies. To accomplish these aims we used 3 cell lines: SKBR3, HCC1954, ZR75-1 and a novel mouse model of HER2-driven mammary carcinoma.

We treated tumor-bearing mice with daily Lapatinib, and two dosing regimens of Trastuzumab (high and low dose). Lapatinib therapy led to tumor regression. However, there was stabilization tumor, but no regression in the high doses group and no response in the low dose Trastuzumab. The response to Lapatinib demonstrates HER2 addiction and confirms the translational relevance of the mouse model. Next, we treated each cell line with different concentrations of Lapatinib for different periods of time to assess changes in c-Myc and p-HER2. As expected, we observed a concentration and time-dependent reduction in the phosphorylation of HER2 with Lapatinib treatment. Interestingly, in one cell line (SKBR3), c-Myc levels rose as p-HER2 levels fell in response to Lapatinib treatment. Finally, we compared the growth and Lapatinib-response of cell lines expressing shRNA to c-Myc or a non-targeted shRNA control. Although our knockdown was variably successful, preliminary data suggest that HER2-positive cell lines expressing greater levels of c-Myc are more resistant to Lapatinib therapy (ie. higher IC50 on cell viability assays).

Moving forward we will 1.) repeat our in vitro experiments with new c-Myc shRNA HER2-positive breast cancer cell lines 2.) compare the c-Myc and pHER2 protein levels before and after treatment with Lapatinib in the mouse.
Concentric Tube Robotics: Non-linear Trajectories for Stereotactic Epilepsy Surgery

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Recurrent and unprovoked epilepsy seizures affect more than 50 million people worldwide. Despite advances in antiepileptic drugs, more than 30% of patients continue to demonstrate abnormal neuronal activity; at present, this can only be treated with surgical intervention. In 80% of patients with medically intractable seizures, the epileptic focus is located in the medial temporal lobe and neurosurgical treatment of these foci requires large skin incisions, extensive bone removal, and potentially harmful excision of brain tissue, several times the size of the epileptic focus.

Minimally invasive approaches rely on straight endoscopic cannula to either deliver depth electrodes to further refine the target area or lasers to ablate the epileptogenic tissue. However, straight cannulas struggle to properly access non-linear targets such as the amygdalo-hippocampal region often implicated in medial temporal lobe epilepsy. Furthermore the cannulas must be positioned to avoid critical structures such as blood vessels and cerebrospinal fluid filled ventricles. We propose to overcome the limitations of rigid cannulas by introducing curved concentric tubes to perform non-linear 3D minimally invasive trajectories.

Concentric tube robots are composed of multiple superelastic Nitinol segments arranged telescopically. Each segment can be independently translated and rotated giving rise to two degrees of freedom that can be modelled computationally. Parameterization of the robot characteristics in conjunction with a global pattern search optimization method can determine the optimal trajectory to achieve the greatest coverage of a target volume. Semi-automatic segmentation of MRI images can generate surface models of target structures as well as obtain coordinates for entry points and boundary constraints. In addition, we will introduce weighted constraints for surgically relevant tissues and structures such as ventricular spaces and blood vessels.

We hope to quantify the effectiveness of a multi-segmented concentric tube robot at covering a desired target and compare to a standard rigid cannula approach. We predict a segment number above which no appreciable change in target coverage can be achieved and seek to use these parameters as guidelines to fabricate a prototype concentric Nitinol tube navigation system. We will evaluate the effectiveness of the procedure using 3D printed polymer models of brain tissue and cadaveric specimens. With the aid of MRI image guidance, we can introduce a concentric tube robot through a 5 mm bur hole, navigate the probe into the temporal horn to introduce electrodes or ablate epileptogenic tissue. The concentric tube robotics platform promises an exciting advance in endoscopic neurosurgery.
Assessing the Need for Mental Health Services in UNRWA Clinics in Lebanon for Palestinian Refugees from Syria

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The United Nations Relief and Work Agency (UNRWA) has been the primary, and often the only, body that delivers relief and medical services since 1948 to the Palestinian refugee population relocated to Syria, Lebanon, Jordan, the West Bank, and Gaza. Due to worsening conflicts, the Palestinian refugees were unable to move around safely and faced severe restrictions owing to escalating threats from shelling and armed clashes, exacerbating vulnerabilities that existed prior to the Syrian conflict. While this population suffered from the warfare, no structured mental health services, including psychological counseling, is provided by UNRWA clinics in Lebanon, where a portion of PRS now reside. As there is no mental health diagnosis made, it is unknown as to the extent of untreated patients in this 235,000 refugee population.

This project, thus, is crucial from the healthcare system perspective as seeks to understand the barriers to mental health services and potential solutions from the perspective of the providers providing care to this vulnerable population. The goal is to lay the groundwork for more extensive work addressing the needs of subpopulations at particular risk and to work towards the design of effective interventions to provide services address the mental health of Palestinian-Syrian refugees.

To assess the needs for mental health services, PRS from UNRWA clinics were given the Primary Health Questionnaire 9 (PHQ-9) and the Clinician-administrated PTSD scale (CAPS). A portion of the patients was asked to participate in an in-depth interview, gauging the services they had received and their attitudes toward mental health. Healthcare providers at the UNRWA clinics were also surveyed to assess their perspectives on the infrastructural and organizational barriers in creating mental health services and solutions to those barriers.

To date, 46 PRS had completed the screening questionnaires, of which 5 in-depth interview were obtained. 20 UNRWA healthcare providers had completed the assessment survey. Once the sample size is met, the questionnaire data would estimate the cases of undiagnosed mental illnesses. The qualitative interview and provider survey will be analyzed as themes will be identified and responses will be grouped by themes and ranked.

Although relying screening tools were administrated by healthcare providers, diagnoses of mental illnesses were unable to be made as no psychiatrists were available to diagnosed patients with according to DSM guidelines. Notably, as it is socially unacceptable for men convene weakness, two men had refused to participate this study. Thus, cultural stigmas also posted limitations.
Use of Glycotransferase-Programed Stereosubsitution (GPS) to improve targeted cell therapies in Traumatic Brain Injury

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Traumatic Brain Injury (TBI) is the leading cause of injury related death and disability in the U.S., affecting 1.7 million people annually. In addition, it is a source of major economic loss (> $75 billion/year). The pathophysiological mechanisms that ensue following a TBI are complex. They involve the primary mechanical injury, followed by a wave of neuro-inflammation, excitotoxicity, ischemia and increased intracranial pressure that results in further neuronal cell death. Given the multifactorial nature of TBI, a single drug cannot selectively address all the component processes. This fact prompts the search for solutions that involve stem cell-based therapy.

In the last decade, animal models have implicated the bone marrow-derived human mesenchymal stem cell (hMSC) as a promising tool for treating neurodegenerative disorders and central nervous system (CNS) injuries. hMSCs have been shown to possess anti-inflammatory/immunosuppressive properties, as well as the ability to promote a tissue microenvironment that encourages regeneration by stimulating tissue-resident stem cells to proliferate and differentiate. Unfortunately, successful implementation of hMSC therapy has been largely hindered by our inability to efficiently deliver therapeutic doses via the vascular to the CNS. To tackle this problem, we sought to glycoengineer the hMSCs surface using a novel glycoengineering technology known as Glycosyltransferase-Programed Stereosubstitution (GPS), to enforce expression of the potent E-Selectin Ligand, HCELL. We hypothesize that GPS-modified hMSC will significantly improve cell delivery to sites of damaged brain tissue following a TBI.

To test this hypothesis, we used a controlled cortical impact device to induce TBI in our rat model. At either 6 hours or 5 days following the TBI, rats received a single tail vein injection with fluorescently labeled hMSCs that had either been modified by GPS or had not been modified. All animals were sacrificed 24 hours following stem cell transplantation. Brain tissue was then fixed and later sectioned for inspection by fluorescent microscopy.

We observed that hMSC transplantation 5 days post-TBI resulted in greater delivery to damaged brain tissue compared to injection at 6 hours post-TBI. However, compared to injection of unmodified cells, the GPS-modified cells showed no increase in cell delivery at injury sites. We are currently working on obtaining objective quantitative data for each group. It is possible that when transplanting GPS-modified hMSC, a carotid artery injection may be more advantageous. This route bypasses other tissue sites that may be competing for cell recruitment.
Is Use of Biomass Fuel Associated with Anemia in Pregnant Women in Nagpur, India?

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Background: Anemia in pregnancy (AIP) affects upwards of 50% of pregnant women in developing countries and is associated with adverse outcomes for mother and child. Major factors that contribute to AIP are physiologic changes in pregnancy and folate and iron deficiency. We hypothesized that exposure to smoke from biomass fuels (wood, straw, crop residues, or dung) – which are widely used in households in resource-limited settings – could exacerbate AIP, possibly as a result of chronic inflammation.

Objectives: This study sought to 1) determine the prevalence of AIP, classified by severity, in women who use biomass fuel for cooking as compared to women who use clean fuel (electricity, liquefied petroleum gas, natural gas, or biogas), and 2) evaluate whether exposure to biomass smoke is an independent risk factor for AIP.

Methods: A secondary data analysis was conducted using data collected from a pregnancy cohort (N=13,345) in Nagpur, India in 2011-2013 as part of the Maternal and Newborn Health Registry Study of the NIH-funded Global Network for Women and Children’s Health Research. Women were classified based on hemoglobin (Hb) level as not anemic (Hb ≥ 11 g/dl), mildly anemic (10 g/dl ≤ Hb < 11 g/dl), or moderately-to-severely anemic (Hb < 10 g/dl). Multinomial logistic regression was used to estimate the effect of exposure to biomass vs. clean fuel on AIP, controlling for maternal age, BMI, educational level, trimester when hemoglobin was measured, parity, exposure to household tobacco smoke, and receipt of prenatal iron supplementation.

Results: The prevalence of any anemia was 93% in biomass fuel users and 88% in clean fuel users. Moderate-to-severe AIP occurred in 53% and 40% of the women, respectively. Multinomial logistic regression showed higher odds of mild AIP (RRR = 1.29, 95% CI = 1.13-1.46) and of moderate-to-severe AIP (RRR = 1.83, 95% CI = 1.60-2.08) in biomass vs. clean fuel users, after adjustment for covariates. Of the covariates included in the regression model, all except receipt of prenatal iron supplements were significantly associated with mild and/or moderate-to-severe AIP.

Limitations: The main limitation of this study is that the only available measure of socioeconomic status was educational level; consequently, there may be residual confounding by socioeconomic status.

Conclusions: In our study population, biomass fuel use was associated with higher risks of mild and moderate-to-severe AIP, independent of maternal age, BMI, educational level, trimester when hemoglobin was measured, parity, and exposure to household tobacco smoke.
Effects of Institutionalized Care on Aggressive Behavior

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The Bucharest Early Intervention Project (BEIP) is a prospective cohort study in which institutionalized children were randomized into two groups at a young age, either to remain in institutions or to receive foster care, and followed over time. Comparisons between the groups and with community controls allow the unique opportunity to examine how development is influenced by early psychosocial deprivation.

The conceptual framework that underpins BEIP is that psychosocial deprivation early in life can lead to abnormalities in child development, ranging from cognitive functions to socio-emotional behavior to mental health. Furthermore, many other studies have found that early abnormal social responses can later lead to aggression and delinquent behavior. A better understanding of childhood aggression and can shed light on potential interventions.

I hypothesized that children in the ever institutionalized group (EIG) would have greater aggression than never institutionalized group (NIG), and children randomized to continued care as usual in the institution (CAUG) would have greater aggression than the foster care group (FCG).

To assess levels of aggression, I analyzed questions related to aggression taken from teacher Health and Behavior Questionnaire (HBQ) of children at 8 years. Questions were separated into four categories: physical bullying, verbal bullying, property victimization, and psychological aggression. Data were analyzed using IBM SPSS Statistics, version 19.

While there is significant difference in aggression levels between the EIG and NIG groups ($p < .05$), there appears to be no significant difference between aggression scores in the FCG and CAUG groups for any of the categories of aggression.

These findings are consistent with previous data showing no improvement in externalizing behaviors in the FCG group at 54 months and in executive functions in 8 year olds. No difference in aggression between the FCG and the CAUG in the face of clear differences between EIG and NIG could be due to several factors. One possibility is that the time of intervention occurred after the sensitive period during which aggression is developmentally suppressed. However no conclusive statements can be made without further studies.

The method of data collection inevitably introduces reporter bias. Institutional caregivers cannot consistently be present around the children, and therefore may miss certain tendencies the children display. Furthermore, foster parents may hold varying standards for their children, introducing variability. Thus, it is difficult to directly measure the relationship between individual quality of care and outcomes.
Factors associated with survival in patients with oligometastatic non-small cell lung cancer (NSCLC)

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Although palliative chemotherapy is the standard of care for metastatic NSCLC, some patients with oligometastatic disease may benefit from aggressive local therapy. We investigated factors associated with longer survival among patients presenting with up to five metastatic lesions to better characterize those patients who may derive such a benefit.

We identified patients presenting with Stage IV disease at diagnosis of NSCLC who were prospectively consented and enrolled in our institutional database from 2002-2011. Based on criteria from recent SBRT series, we defined oligometastatic disease as five or fewer discrete metastatic lesions on PET and/or MRI that were present synchronously at time of initial staging. Univariable and multivariable Cox proportional hazards models were used to analyze factors associated with overall survival among this cohort.

We identified 206 patients (20.1% of Stage IV patients) that met our criteria for oligometastatic disease. Median age at diagnosis was 61.2 years, 50% of patients were female, 65% had adenocarcinoma histology, and 32% had N0-1 disease. 38% had brain metastases, 41% had bone metastases, and 79% had a single organ involved with metastases. The median survival from date of diagnosis was 18 months (mos). On univariable analysis, longer overall survival was associated with ECOG performance status 0-1 vs 2+ (median 18.7 vs 9.7 mos, HR 0.43, p<.01); N stage N0-1 vs N2-3 (33.0 vs 15.5 mos, HR 0.49, p<.01); adenocarcinoma vs non-adenocarcinoma histology (19.6 vs 13.8 mos, HR 0.68, p=.02); and number of organs with metastatic involvement (overall p=.02). Number of metastatic lesions (overall p=.09) and weight loss ≤2 vs >2 kg (HR 0.75, p=.10) approached significance. On multivariable analysis, ECOG 0-1 (HR 0.52, p=.05); adenocarcinoma (HR 0.59, p<.01); N stage N0-1 (HR 0.39, p<.01); and a single metastatic organ (HR 0.54, p<.01) were associated with longer survival.

Potential selection bias existed among patients who received and did not receive aggressive treatment. Also, a single-institution, retrospective study is prone to bias.

In conclusion, select patient and tumor characteristics, including good performance status, adenocarcinoma histology, limited nodal disease, and metastatic involvement of a single organ, may predict for improved survival among patients with oligometastatic NSCLC. Future studies will evaluate the impact of aggressive local therapy in these patients.
Perception of a Profession: Viewing Dentistry through Pictures and Popular Images

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The current incarnation of the profession of dentistry in America has been greatly shaped by the past, particularly by extensive changes in education, regulation, technology, and materials during the nineteenth century. The mid-1800s saw the establishment of the first dental schools, the founding of dental associations, the first published dental journals, and the introduction of anesthetics. The drive to regulate and standardize the profession was influenced by forces both from within and outside of dentistry.

I sought to determine how these changes contributed to the evolution of the public perception of dentistry through examining popular images of dentists and the dental profession. These images, at one level, reflect the artists’ and presumably the public’s perceptions of the profession. At the same time, paintings, drawn images, and photographs can influence opinions of dentistry itself.

To determine how the profession of dentistry has evolved over the 1800s, I researched the training, standard practices, regulations and legislature, and official organizations of dentists through secondary sources, dental journals, and annual reports and speeches of the ADA and dental schools.

To determine how changes in the profession of dentistry are reflected in public opinion and popular images, I examined images of dentists from the nineteenth century from the archives of the National Medical Library, the Library of Congress, and the Countway Medical Library. In order to understand the social and historical context of the pieces, I looked in particular at who commissioned the art, who was the intended audience, and what was the purpose of the image. I also analyzed the stylistic choices in the image, facial expression, patterns in symbols and imagery, and other aspects that inform the viewer about the subjects.

Print media and popular images both chronicle popular perceptions and knowledge of dentistry, as well as influence and direct public opinion. By understanding the history of the dental profession and putting images into social context, we can explore the evolution of the profession through the intersection of social history and art.
Frequency of Synovial Cysts of the Temporomandibular Joint at Massachusetts General Hospital

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Synovial cysts are lesions containing the synovial fluid from a bordering joint and lined with synoviocytes. These lesions are frequently found on the extensor surface of the wrist, and the dorsal surface of the foot and knee, but also present in the temporomandibular joint (TMJ). Gaisford et al. reported the first description of a synovial cyst of the TMJ in 1969 and the literature has only reported 13 occurrences through 2013. The low incidence of TMJ synovial cysts has prevented establishment of a standard of treatment. The prevalence of reported ganglion cysts, pseudocysts with an acellular fibrous tissue lining, is significantly higher than the number of synovial cysts present in the literature and therefore there is more conclusive data for their origin and treatment. The precise therapy and surgical treatment for synovial cysts of the TMJ is uncertain due to rare evidence in the literature, however, there is an impression in our MGH practice that this prevalence is underestimated and not a reflection of the true prevalence of the lesions. A cohort of patients composed of all subjects evaluated and treated with synovial (or ganglion) cysts at MGH was examined to estimate and compare the prevalence of synovial and ganglion cysts of the TMJ versus extra-cranial synovial and ganglion cysts, as well as to identify radiographic and clinical findings that might be useful in their differentiation, and to compare clinical outcomes between the two. A cohort of 12 patients with synovial cysts of the TMJ and 2 patients with ganglion cysts of the TMJ at MGH was identified and evaluated with a number of clinical variables. The prevalence of synovial cysts of the TMJ was 0.8% and ganglion cysts of the TMJ was 0.1%, indicating a higher synovial prevalence than what was previously reported. The study is limited by the small patient cohort and missing follow up records from a number of patients. We are currently working with the pathology department to confirm the diagnosis of our current patients with synovicyte-specific dye (D240). Once, the diagnoses are confirmed, we will analyze our variables. We hope that this will enable us to gain more information on etiology, presentation, diagnosis, and treatment outcomes, with the goal of developing a more standardized management of these patients.
Surgical care delivery and operative capacity at the major academic referral hospital in Liberia

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**Background:** Global surgical disease burden, estimated at 11-15% of total disability adjusted life years (DALYs) lost worldwide, is known to disproportionately affect low- and middle-income countries (LMICs), where the inadequacy of surgical and anesthetic capacity is well-demonstrated. Further, situational needs of health care facilities inform the optimal allocation of resources and quality improvement efforts. This study examines metrics of surgical care delivery at a tertiary care institution in Liberia.

**Methods:** We retrospectively reviewed operative and ward logbooks from January 1 to December 31, 2012. Data parameters included patient age, diagnosis, procedure, mortality outcome, length of stay, out-of-pocket patient costs and perioperative provider information.

**Results:** In 2012, 1036 operations were performed. Adults comprised 72% (749/1036) of surgical patients and 23% of adult cases were emergent. General surgical procedures predominated in adults (45%) and over half of these were exploratory laparotomies, appendectomies or herniorrhaphies. Orthopedic (20%) and ophthalmologic procedures (18%) also accounted for a significant portion of all cases. Of pediatric cases, 30% were emergent and approximately 9% were temporizing procedures for hydrocephalus. Ward logs documented 6.5% in-hospital deaths among surgical patients, over half of which occurred after exploratory laparotomy (39%) and in burn (14%) patients. General, spinal, and TIVA anesthesia was provided by non-physician personnel. Sixty-one percent of patients paid out-of-pocket for costs incurred due to surgery. Procedure charge to patients varied from 27 USD for herniorrhaphy to 201 USD for open prostatectomy. Free care was provided to 35% of patients, including all children under age 5 and those deemed to have extenuating circumstances by a social worker. Insurance covered care for an additional 4% of patients.

**Conclusions:** A significant portion of operations was performed emergently. Orthopedic and ophthalmologic operations required specialty surgeons, while general surgeons performed most urologic and neurosurgical procedures. High surgical mortality in the immediate postoperative period demonstrates a pressing need for ICU facilities. Given that most surgical care is provided by medical officers and nurse anesthetists, the country's effort to begin a professional accreditation system will be helpful in increasing the number of board-certified providers and aligning training metrics with situational needs. Cost for essential surgery in Liberia remains significant relative to per capita GDP (490 USD per year). Accurate costing of surgical procedures in LMICs may help maximize access to certain lifesaving and highly cost-effective operations. In addition, improved outpatient wound management may decrease lengths of stay and drive down patient out-of-pocket costs for hospitalization.
Measuring the Effects of Treating Major Depressive Disorder (MDD) with Repetitive Transcranial Magnetic Stimulation (rTMS): A Naturalistic Study

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In 2008, the FDA approved the use of repetitive transcranial magnetic stimulation (rTMS) for the treatment of depression after it was shown to be an effective treatment. rTMS is a non-invasive technique for stimulating the brain that generates a brief, high-intensity oscillating magnetic field directly above the targeted brain area with a magnetic coil. To further study the effects of rTMS, McLean Hospital participates in a patient registry study that prospectively follows the effects of rTMS treatment as measured by validated self-assessment scales.

In this study, we chose to measure the effects of rTMS on depression as measured by the Quick Inventory of Depressive Symptomatology (QIDS) scale and on social and work functioning as measured by the Work and Social Adjustment Scale (WSAS). Prior evidence indicates that rTMS reduces depression symptoms over the course of treatment, so we hypothesized a reduction in QIDS scores. Similarly, since lower WSAS scores indicate better work and social functioning, we hypothesized a trend towards lower WSAS scores.

Subjects were enrolled in this naturalistic study at McLean Hospital and QIDS and WSAS self-assessments were collected at baseline and weekly for five weeks while treatment lasted. Although eight subjects were enrolled, only two subjects had completed treatment at the time of analysis.

Subject 1 is a white female with a history of 5-10 depressive episodes and more than two treatment failures. From baseline to the end of treatment, her available weekly QIDS scores were 12, 8, 7, 11, and 10, while her available weekly WSAS scores were 24, 20, 25, and 23. Subject 2 is a white female with a history of more than 12 depressive episodes and more than two treatment failures. From baseline to the end of treatment, her weekly QIDS scores were 16, 6, 10, 4, 6, and 7, while her WSAS scores were 31, 26, 18, 14, 16, and 32.

Both subjects saw a decline in their depression symptoms from baseline to post-treatment as measured by QIDS, a result that is consistent with existing literature on the effects of rTMS. Subject 2’s WSAS scores showed a large decreasing trend except for the last week, while Subject 1’s WSAS scores varied only slightly throughout treatment. Further analysis should be made when more subjects have completed both the treatment and follow-up phases of the study to overcome the small sample size and time window limitations of this study.
Radiation Therapy for Pediatric Solid Malignancies in the Dominican Republic

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Approximately 200,000 children around the world are diagnosed with cancer each year, and it is estimated that 80% of them live in low/middle income countries (LMIC). In these countries, the resources and knowledge about how to treat and palliate cancer are limited. High income countries (HIC) have access to technologies and treatments that have improved survival rates to over 80% for many pediatric cancers. Collaborations, or twinning programs, between doctors from established programs and clinics developing their programs have been established to disseminate knowledge and to build the capacity for cancer treatment even in regions of the world with few resources. Thus far, twinning programs have been extremely successful at reducing mortality due to hematologic malignancies, but progress on solid tumors has been slower. We believe that because radiation therapy is frequently required for solid malignancies, but not for hematologic cancers, that this procedure contributes to the minimal improvement. Radiation therapy is intricate, and requires a well-trained, multi-disciplinary team. It also requires functional equipment and is influenced by psychological and social factors that may lead to treatment abandonment. Currently, there are no studies addressing in detail the quality of radiation therapy available and delivered to children with pediatric tumors in countries with limited resources.

The goals of this monitoring and evaluation study are to measure the program’s ability to adhere to protocol, to analyze the available resources, and to identify the additional challenges experienced in low-resource communities. We collected 50 charts of patients with common solid malignancies in the Dominican Republic (rhabdomyosarcoma, Wilms Tumor, nasopharyngeal carcinoma, and retinoblastoma) and compared their course of treatment with disease-specific radiation therapy protocols which have been adapted based on predicted resource availability. We will also assess the utilization of available resources (including the number of Linear Accelerators versus Cobalt machines, the usage of public versus private facilities, and the distance from patient’s home to treatment center). Data on the timing of surgery and the completeness of pathology reports was collected secondarily. This will be a pilot project not only to identify potential areas of improvement for the Dominican Republic, but also to develop the methods necessary to create a program assessment tool, which can be applied to programs in other low-resource settings.
A Population-Based Strategy for Mental Health and Primary Care Integration

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One quarter of American adults suffer from mental health and substance use disorders (MH/SUD) every year, and it is estimated that primary care providers manage between 40-80% of these patients. Unfortunately, rates of detection and adequate treatment in the primary care setting are currently suboptimal, leading to poor disease management and driving excess utilization. Improved delivery of MH/SUD services in the primary care setting is critical for improving quality and lowering costs. Over the past decade, researchers from across the country have developed evidence-based strategies for treating specific mental health disorders in primary care. Achieving the full health and economic benefits of integrating MH/SUD and primary care services requires combining these discrete strategies into a coordinated approach that can be implemented at scale across entire primary care populations.

To accelerate this transformation, we have developed a comprehensive clinical service model that embeds social workers and psychiatrists into primary care practices to offer integrated care for depression, anxiety, and SUD. The model is built around five core tactics: 1) enhanced detection 2) coordinated MH/SUD and primary care services 3) evidence-based care protocols 4) streamlined access to specialty care and 5) comprehensive monitoring and follow-up. These tactics are deployed according to a risk stratification framework that directs additional services to medically complex patients at risk of being high cost. Randomized controlled trials and meta-analyses have shown that service delivery models that employ many of the tactics above improve detection and treatment for anxiety, depression, and SUD in the primary care setting.

Improved access to coordinated, evidence-based MH/SUD services has the potential to reduce inpatient, emergency department, and outpatient psychiatric services associated with poor management of MH/SUD and co-morbid illness. To investigate this relationship, we constructed a financial model to project the impact of integrated MH/SUD services on health care utilization and total medical expense (TME). When implemented at scale across a large primary care network serving ~400,000 patients, the proposed model is projected to reduce cumulative 3-year TME by 0.42%, generating $38,694,335 in savings. Based on an estimated cost of implementation of $18,194,604, this represents a return on investment of 2.12 to 1. This analysis suggests that the proposed model is a financially sustainable path for MH/SUD and primary care integration under alternative payment contracts that reward providers for reducing medical expense and improving outcomes.
Health systems strengthening through HIV treatment scale-up: A ten year review of the Rwandan experience

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Since the genocide, Rwanda has undergone a remarkable transformation. It has ushered in some of the highest levels of economic growth in Africa, significantly reduced extreme poverty, prevented the recurrence of mass violence, and raised life expectancy from 48 years in 1990 to 62 years in 2010 for men, recovering from a low of 28 years during the genocide. This rapid rate of progress has been no less true in the realm of HIV/AIDS treatment. Though in 2002 the prohibitive cost of medicines resulted in only an estimated 870 people receiving treatment, just ten years later, Rwanda had managed to place 115,000 people on HIV treatment free at the point of delivery. This represented 91.5% coverage of people eligible for treatment, making Rwanda one of two African countries to achieve the United Nations goal of universal coverage. Mortality associated with HIV disease fell by 78.4%, the greatest reduction in the world from 2002-2012. Not many would have expected a country like Rwanda to recover its health system from the destruction of the genocide, let alone achieve universal treatment coverage for a disease as complex as HIV/AIDS. This paper seeks to explain these outcomes by analyzing three critical themes of the Rwandan health system: accountability, accessibility, and the efficient use of funding to strengthen the health system. First, this paper will review the evidence on HIV/AIDS treatment outcomes within Rwanda and explain how leadership and governance at the national and local levels have formatively shaped Rwanda’s HIV/AIDS achievements. The next section reviews the strategic measures taken by the Government of Rwanda to improve geographic and economic accessibility to the health system. The final section describes the strategies the Government of Rwanda has employed to use HIV/AIDS funds to strengthen its broader health system without sacrificing quality of care for HIV/AIDS patients.
Functional Characterization of a Novel Genetic Locus for Plasma Cholesterol

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Genome-wide association studies (GWAS) have identified a number of novel genetic loci linked to serum lipid levels. The causal DNA variants at these loci and the mechanisms by which they influence phenotype and disease risk remain largely unexplored. Expression quantitative trait locus (eQTL) analysis of patient liver and adipose biopsies indicates that many lipid-associated variants influence gene expression in a cis-regulatory manner. However, linkage disequilibrium among neighboring SNPs at a GWAS-implicated locus makes it challenging to pinpoint the causal variant underlying an association signal. To address this issue, we and our collaborators performed a massively parallel reporter assay (MPRA) to identify potentially causal SNPs at 57 eQTL loci associated with lipids. From the MPRA data, we prioritized variants that displayed significant regulatory activity, as measured by reporter expression, in cultured murine adipocytes. The highest priority variant, rs2277862, exhibited significant allele-specific regulatory activity and is associated with total cholesterol levels in humans. We hypothesized that rs2277862 is causal for the eQTL at the 20q11 locus and that it lies within a transcriptional enhancer site that influences nearby gene expression.

We utilized a novel genome-editing technology in human pluripotent stem cells (hPSCs) to generate isogenic cell lines that differ only at the SNP of interest. The main advantage of this approach is that the cell lines are genetically matched except at the locus of interest, eliminating the effect of differing genetic backgrounds on gene expression. We used the CRISPR/Cas system to either disrupt the putative enhancer site or knock in the alternate SNP allele. For the former approach, we used an hPSC line heterozygous for the minor allele, which is predicted to increase enhancer activity, and generated indels surrounding rs2277862 at a frequency of 60%. For the latter approach, we used a homozygous major hPSC line and, with a donor template, knocked in one copy of the minor allele at a frequency of 0.15%.

We will differentiate the modified hPSC lines into adipocytes and compare expression of transcripts within 300 kb of rs2277862. This locus harbors several genes with no previous connection to lipid metabolism, including ERGIC3, CPNE1, and CEP250. If we detect differential gene expression between the lines, we will seek to identify the transcription factor(s) that binds the putative enhancer site to mediate these allele-specific effects. We anticipate that this project will offer fresh insight into the mechanism by which GWAS-implicated SNPs influence expression of causal genes for lipid metabolism.
Baseline Spin-Echo Echo-Planar Perfusion Imaging Prior to Chemoradiation is a Strong Independent Predictor in Newly Diagnosed Glioblastoma

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Glioblastoma is the most common primary brain tumor in adults, and it is associated with a dismal prognosis. While patient survival varies widely, it is influenced strongly by patient age, performance status, completeness of resection and other factors. To assess whether spin echo echo-planar perfusion weighted imaging (SE-PWI) before and after initiating chemoradiation can stratify patients with respect to progression free survival (PFS) and overall survival (OS).

Approval for this retrospective Health Insurance Portability and Accountability Act compliant study was obtained from the institutional review board. Sixty-eight patients (mean age 58.3, 36 males) were included in analysis. Spin-echo echo-planar cerebral blood volumes (SE-CBV) in enhancing and nonenhancing tumor, normalized to contralateral normal appearing white matter (SE-nCBV), were assessed at baseline and after initial chemoradiation in sixty-eight newly diagnosed glioblastoma patients. SE-nCBV parameters predictive of PFS and OS were identified by univariate and multivariate Cox proportional hazards modeling.

Multivariate analysis demonstrated that baseline tumor mean SE-nCBV was predictive of PFS (p=0.038) and OS (p=0.004). Within the patient sample, baseline tumor mean SE-nCBV < 2.0 predicted longer patient PFS (median 47.0 weeks, p<0.001) and OS (median 98.6 weeks, p=0.003) compared with baseline mean SE-nCBV ≥ 2.0 (median PFS 25.3, median OS 56.0 weeks). Exploratory multi-group stratification demonstrated that very high ( > 4.0) tumor SE-nCBV was associated with worse patient OS than intermediate high (≥2.0, < 4.0) SE-nCBV (p=0.025).

Baseline mean SE-nCBV can stratify patients for PFS and OS prior to initiation of chemoradiation, which may help select patients who require closer surveillance. Our exploratory analysis indicates a magnitude-dependent relationship between baseline SE-nCBV and OS.
Retrospective study of using carmustine or lomustine with bevacizumab in recurrent glioblastoma patients who have failed prior bevacizumab

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Glioblastoma is the most common primary brain tumor in adults, and it is associated with a dismal prognosis. Despite standard treatment involving surgery, chemotherapy and radiation, patients inevitably have recurrent disease. There are currently no known effective treatments for recurrent glioblastoma once patients progress on a bevacizumab-containing regimen. We examined the efficacy of adding nitrosureas to bevacizumab in patients who progressed on an initial bevacizumab-containing regimen.

In this retrospective study, adult patients with histologically confirmed glioblastoma (W.H.O. grade IV) who were treated with lomustine or carmustine in combination with bevacizumab as a second or third bevacizumab regimen after failing an alternative initial bevacizumab-containing regimen were identified. Response rate (RR), six-month progression free survival (PFS6), and progression-free survival (PFS) were assessed for each treatment.

Forty-two patients were identified (28 males) with a median age of 49 years (range 24-78). Of 42 patients, 28 received lomustine (n=23) or carmustine (n=5) with bevacizumab as their second bevacizumab-containing regimen, and 14 received lomustine (n=3) or carmustine (n=11) as their third bevacizumab-containing regimen. The median PFS (mPFS) was 44 days, significantly decreased in comparison to mPFS (114 days) during initial bevacizumab-containing regimen (p=0.0001, by log-rank). Relative to the initial bevacizumab-containing regimen, patients receiving bevacizumab and a nitrosurea on a subsequent regimen had a significantly decreased RR (0% vs. 41%, p<0.001) and PFS-6 (3% vs. 26%, p=0.038) despite increased grade 3-5 toxicity (45% vs. 19%, p=0.010). Median OS was 18.7 weeks from time of nitrosurea-containing bevacizumab regimen initiation.

Despite the limitations of our study, it provides insight into the clinical practice of adding nitrosurea agents to bevacizumab after a patient has progressed on an initial bevacizumab-containing regimen. While bevacizumab may be an effective treatment as an initial regimen in recurrent glioblastoma, its continuation with the addition of a nitrosurea was not an effective salvage therapy for the majority of patients despite additional toxicity.
Volumetric Assessment of Magnetic Resonance Imaging in Recurrent Glioblastoma Patients Treated With Bevacizumab

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Glioblastoma is the most common primary brain tumor in adults, and it is associated with a dismal prognosis. Despite standard treatment involving surgery, chemotherapy and radiation, patients inevitably have recurrent disease. While there is a high radiographic response rate in patients with recurrent glioblastoma following bevacizumab therapy, survival benefit has been relatively modest. We assess whether tumor volume measurements based on baseline and early post-treatment MRI can stratify patients in terms of progression-free survival (PFS) and overall survival (OS).

Baseline (-4 +/- 4 days) and post-treatment (30 +/- 6 days) MRI exams of 93 patients with recurrent glioblastoma treated with bevacizumab were retrospectively evaluated for volume of enhancing tumor as well as volume of the T2/FLAIR hyperintensity. Overall survival (OS) and progression-free survival (PFS) were assessed using volume parameters in a Cox regression model adjusted for significant clinical parameters.

In univariable analysis, residual tumor volume, percentage change in tumor volume, steroid change from baseline to post-treatment scan, and number of recurrences were associated with both OS and PFS. With dichotomization by sample median of 52% change of enhancing volume can stratify OS (52 weeks vs. 31 weeks, p=0.013) and PFS (12 weeks vs. 21 weeks, p=0.009). Residual enhancing volume, dichotomized by sample median of 8cm³, can also stratify for OS (64 weeks vs. 28 weeks, p<0.001) and PFS (21 weeks vs. 12 weeks, p=0.036).

Volumetric percentage change and absolute early post-treatment volume of enhancing tumor can stratify survival for patients with recurrent glioblastoma receiving bevacizumab therapy. Although results will need to be validated in a prospective study, these results indicate promise for utilizing volumetric analysis to identify recurrent glioblastoma patients likely to receive a durable benefit from bevacizumab therapy.
A community-based needs assessment of the Navajo food environment: Understanding barriers to healthy food access

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Over the past several decades, the burden of disease in American Indian (AI) populations has shifted from epidemics of infectious diseases to diet-related chronic diseases. The Navajo Nation is the largest AI tribe in the United States with some of the highest measures of chronic disease in the country, including a diabetes prevalence of greater than 40% in Navajo older than 45 years. The rising rates of chronic disease are, in part, driven by rising rates of food insecurity, exacerbated by widespread poverty and limited access to care. To support the growing movement to improve access to healthy foods in Navajo Nation, we sought to better understand food security in this community through in-depth interviews with tribal members.

As part of a larger mixed methods study to understand food security in Navajo Nation, we conducted a qualitative needs assessment to explore: 1) the factors that drive the food choices made by community members, as well as 2) the feasibility of an intervention to make healthy foods commercially available at Chapter Houses (community centers). In partnership with the Navajo Nation Community Health Representative Program, we used community-based participatory research methods to develop the interview guide. Twenty-five in-depth interviews were conducted from January – June 2013 with Navajo tribal members: 5 local officials, 6 Community Health Representatives, and 14 heads of households. Interviews lasted between 60-120 minutes. Interviewees were compensated $25.

A grounded theory approach was used to code the data and generate five categories: structural barriers to healthy food access, individual barriers to healthy food access, enablers to accessing healthy foods, food purchasing strategies, and intervention ideas. Commonly cited structural barriers included unemployment, geographic isolation, and access to utilities. Local officials were notably more likely than heads of households to cite individual barriers to accessing healthy food, which included stigma of asking for help and limited knowledge of food preparation. From further analysis of the categories, preliminary themes emerged including prioritization of other basic needs over food, lack of agency, and the value of community support as a safety net in times of low food security. Data analysis is ongoing.

The barriers to accessing healthy foods in Navajo Nation are complex and deeply rooted in poverty. This analysis will contribute to a deeper understanding of the determinants of community members’ food choices and will enable us to design a community-based intervention in order to overcome the barriers confronted by the community. We hope that such an intervention could be applicable for other AI rural communities as well.
Evaluating the Sequelae of Two Neurosurgical Treatments on Neurocognitive Development in Ugandan Infants with Post-Infectious Hydrocephalus

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Hydrocephalus is associated with a number of neurodevelopmental deficiencies due to diffuse cortical and subcortical damage from continuous ventricular enlargement and elevated intracranial pressure (ICP). Uganda, one of the poorest countries in the world, is a small, land-locked country located in sub-Saharan Africa, where the incidence of hydrocephalus is high due to high birth rate and a high rate of neonatal infection. Shunt dependence, the current standard of care, is risky in this context. Previously, endoscopic third ventriculostomy/choroid plexus cauterization (ETV/CPC) has been shown to be highly effective in preventing shunt-dependence.

However, whether one surgical technique is superior in optimizing neurocognitive development in post-infectious hydrocephalus (PIH) patients is unknown. Additionally, it is not known whether neurocognitive development correlates with volumetric measurements of the brain and cerebral spinal fluid (CSF) in PIH patients. Thus, the goals of this project are to develop and assess metrics that can be used to evaluate the neurocognitive sequelae of these PIH treatments.

Based on preliminary data collected by our group from Ugandan myelomeningocele infants we hypothesized that brain volume would be inversely correlated to both CSF volume and a previously established, linear approximation of ventricular size known as the frontal-occipital horn ratio (FOHR), both determined by CT scans. Further, we also hypothesized that preoperative brain volume would correlate with the preoperative developmental status, assessed with the Bayley Scales of Infant Development III (BSID-III). Finally, we predicted that BSID-III scores would also be inversely correlated to FOHR and CSF volume measurements.

To test these hypotheses, Ugandan PIH patients less than six months of age who live within a controlled distance from CURE Children’s Hospital of Uganda underwent preoperative assessment with administration of the BSID-III to assess neurocognitive status and CT scans to assess brain and CSF volumetrics. Preliminary data are currently being collected and the results from the first 20 patients will be presented.
Adapting a measure of patient- and family- experience to a child and adolescent inpatient psychiatric setting at Boston Children’s Hospital

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Patient- and family- involvement and experience in healthcare services has been a central theme of recent quality improvement efforts in the care of children and adolescents. However, there is a lack of adequately designed and validated instruments evaluating users' satisfaction with child and adolescent (pediatric) mental health services. Although several instruments have recently been shown to have adequate psychometric properties in pediatric outpatient psychiatric settings, there are no validated instruments tailored to the inpatient pediatric psychiatric setting.

Through a literature review on child psychiatry and user satisfaction, the freely available Experience of Service Questionnaire (ESQ) was identified as an instrument that could be modified to assess patient and parent/guardian user satisfaction at The Julius Richmond Inpatient Psychiatry Service (“Bader 5”) at Boston Children's Hospital (BCH). Validated across 41 mostly outpatient pediatric mental health settings, ESQ measures two domains of satisfaction: satisfaction with the (1) care (e.g. interactions with clinicians) and (2) environment (e.g. appointment times and facilities).

Our study aims to assess the validity, reliability, and feasibility of the modified ESQ (mESQ) given to families who have received services on Bader 5. In this ongoing study, the mESQ (developed in consultation with the Psychiatry Quality Program and IRB at BCH and families receiving services from Bader 5 between June-July 2013) is being mailed to patients (ages 9-18) and parents/guardians post-discharge from Bader-5 on a rolling basis. Based on the original ESQ format, we developed a separate mESQ for children ages 9-11, adolescents ages 12-18, and parent/guardians. The questions in the parent/guardian and child versions of the mESQ are similar in content to one another, but language was modified for age-appropriateness.

Data from survey responses will be analyzed to assess three survey validation parameters: (1) feasibility will be assessed by using a multivariable logistical regression model to see how survey participation may be impacted by demographic and clinical data (obtained from patient charts); (2) reliability will be determined by using the intraclass correlation coefficient by having a subset of the participants fill out the survey twice; (3) validity will be established by using confirmatory factor analysis to see if/how the two domains of care identified in the ESQ (i.e. care and environment) fit our sample. Results from this study may allow us to validate our survey instrument for more widespread use in national and global inpatient child and adolescent psychiatry settings.
Inducing Oxidative Damage to Enhance Tyrosine Kinase Inhibition in EGFR-mutated Non-Small Cell Lung Cancer

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Lung cancer is the most deadly cancer in America and worldwide, killing six million people globally per annum. It is not the most frequently diagnosed cancer in either sex, but is diagnosed at metastasis in 70% of cases. Non-small cell lung cancer (NSCLC) is the most frequently occurring type of lung cancer, and the most common mutation associated with NSCLC is in the gene Epidermal Growth Factor Receptor (EGFR). Tyrosine kinase inhibitors (TKIs), such as Gefinitib, target the mutated structure of EGFR; TKIs block the activity of the EGFR kinase from triggering signal transduction pathways driving cancer growth and proliferation.

Development of resistance to targeted therapies for NSCLC occurs in 100% of cases, usually within 10-14 months of initiation. Cells develop secondary mutations that prevent TKIs from binding to EGFR, or gain the ability to proliferate without EGFR signaling. Because of the development of resistance, the average survival time after diagnosis is only prolonged from one year on gold-standard chemotherapy to two years on TKI. If patients with resistance to TKIs take a hiatus from therapy, their tumors re-sensitize to TKI but may grow in the interim. One potential approach may be to give cycles of targeted therapies and alternate with other drugs to minimize tumor growth, or ultimately apply a selective pressure on the tumor to kill additional cancer cells.

Inhibition of glutaminase, the precursor of glutathione, is a highly researched strategy for evading resistance to TKIs, as metabolic profiling of cells subject to TKIs reveals reduced glutathione levels. Glutathione is a scavenger of reactive oxygen species (ROS) in cells; without it, oxidative damage may tip cells onto the path of apoptosis. In vitro studies on adjuvant glutaminase inhibition seem effective, though in vivo work in mice shows no benefit of glutaminase inhibition. The discrepancy may be due to the different metabolism induced in the hypoxic tumor with an oxygen pressure ~ 30mHg, as opposed to the atmospheric oxygen pressure of 158mmHg in in vitro studies. Oxidative metabolism generates ROS, making lower glutathione levels more damaging, whereas glycolytic metabolism observed in vivo may not produce ROS, thus making lower glutathione levels less damaging to cancer cells. This mechanism is explored using hypoxic incubation of EGFR-mutant NSCLC cells with TKI drug cocktails.
Search for novel taxa associated with periodontal health and disease

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Periodontal diseases are initiated and sustained by bacteria, which can cause direct damage to host tissues and elicit potent immune responses. They are characterized by gingival inflammation, bleeding, and bone and tooth loss; periodontitis has been associated with systemic conditions such as cardiovascular disease, diabetes, and low birth weight.

Current knowledge of the etiopathogenesis of periodontal diseases is limited to named cultivated bacteria. However, 50% of the oral microbiota is either unrecognized (not characterized or named) or as-of-yet uncultivated. Thus, unrecognized/uncultivated periodontal pathogens that may contribute to the disease process should be cultivated and characterized. Hence, the aim of this study was to identify the most predominant uncultivated/uncultivated taxa associated with periodontal health and disease that merit cultivation and determined the optimal conditions for cultivating these bacteria for isolation in pure culture.

One hundred probes targeting uncultivated/unrecognized taxa were used to identify the 40 most common (and relevant) taxa based on their prevalence in 16 periodontally healthy and 16 periodontitis patients; this was achieved by the RNA Oligonucleotide Quantification Technique (ROQT), a novel high-throughput technique that quantifies uncultivated/unrecognized microorganisms using oligonucleotide probes. Once identified, they were sought in 5 periodontally healthy and 5 periodontitis subjects and cultivated to achieve optimal growth. Two subgingival biofilm samples were collected from each patient and plated on 5 test agar media (trypticase-soy brain heart infusion, fastidious anaerobe, minimal medium, chocolate, formate-fumarate) and incubated in 3 atmospheres (anaerobic, microaerophilic, capnophilic). After 7 days of incubation at 37°C, plates containing 50-300 colonies were lifted and hybridized with the 40 selected probes; hybridization signals indicated presence and were computed for each sample.

Our results indicated that the target taxa thrived in varying conditions. In healthy individuals, a microaerophilic environment and chocolate agar medium were optimal; in periodontitis patients, an anaerobic environment was optimal, and there were no observed differences among the test media. Minimal media provided the lowest recovery of the test taxa. In the next phase of this ongoing study, the sampling, plating and colony lifting described will be repeated in the same sites/patients to personalize and optimize the individual isolation and characterization of the test taxa. Samples will be plated on the best combination of media and atmosphere observed, isolates that provide a hybridization signal will be transferred a new plate with the same conditions and their identity will be confirmed by ROQT and sequencing.
Qualitative exploration of antenatal and postpartum depression among HIV-infected women in Mbarara, Uganda

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Background: Comorbidity of HIV infection and depression is an important and poorly addressed global problem. 6.5% of Ugandan adults are living with HIV and the prevalence of major depressive disorder among HIV-infected Ugandan adults is 8.1%. Depression among individuals with HIV may decrease adherence to antiretroviral therapy, leading to worse health outcomes. Some studies suggest antenatal and postpartum depression are common among Ugandan women, with deleterious implications for maternal and child health.

The Uganda AIDS Rural Treatment Outcomes (UARTO) cohort follows over 700 HIV-infected men and women in rural, southwestern Uganda. Preliminary data show a decline in depression symptoms (using Hopkins Symptom Checklist, HSCL) during the postpartum period. This finding may be inconsistent with existing literature on the epidemiology of depressive symptoms in postpartum women.

Objectives: The purpose of this study is to explore reasons for reduced depression scores during the postpartum period by exploring the impact of having a child on emotional and psychological wellbeing of HIV-infected women. We hypothesize that, in a society that places a high importance on childrearing and motherhood, HIV-infected women experience great relief upon delivering an HIV-uninfected child, resulting in lower depressive symptomology. The results of this work will help elucidate the utility of the HSCL for this population and inform adaptation for this context.

Study design: Beginning in 2014, we will conduct up to 30 in-depth interviews with female cohort participants with a live birth in the last two years. Interviews will explore emotions and experiences before, during, and after pregnancy. Emergent themes will be further queried through in-depth interviews with health care workers (HCW), and a focus group discussion with the local community advisory board (CAB). Audio-recordings from each phase of the study will be transcribed, coded, and analyzed using content analysis.

Interview guides for each phase have been designed, and translated, and standard operating procedures have been developed for recruitment, enrollment, consent, interviews, and data analysis. Piloting of the participant interview guide generated relevant data and will guide training of the research assistant(s). Eligible HCWs and the local CAB have been identified.

Limitations: Interview questions are broad to provide unbiased data, but may also yield some irrelevant information. HCW interviews will be limited to the 11 HCWS in the Mbarara Hospital Mental Health department. Nevertheless, collecting data from multiple viewpoints should help corroborate the findings.
Incremental Innovation and Regulatory Oversight: Prevalence and Characteristics of Changes to FDA-Approved Cardiac Implantable Electrical Devices

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The US Food and Drug Administration (FDA) evaluates high-risk medical devices, including cardiac implantable electric devices (CIEDs), via the pre-market approval (PMA) process during which manufacturers submit data demonstrating safety and effectiveness. Subsequent changes to these FDA-approved high-risk devices are implemented via “supplements,” which may not require additional clinical testing. The prevalence and characteristics of PMA supplements among CIEDs have not been described.

Using the FDA’s PMA database, we reviewed all CIEDs approved as original PMAs or supplements from 1979-2012. For each supplement, we collected the date approved, type of supplement, and the nature of the changes. We calculated the number of supplements approved per PMA and analyzed trends relating to different supplement regulatory categories over time. For supplements involving major design changes approved from 2010-2012, we identified how often additional clinical data were collected.

From 1979-2012, the FDA approved 77 original and 5,825 supplement PMA applications, with a median of 50 supplements per original (interquartile range [IQR]: 23-87). Excluding supplements for manufacturing changes that do not alter device design, the number of supplements approved each year has remained stable around a mean of 2.6 supplements per PMA per year. PMAs remained active via successive supplements over a median period of 15 years (IQR 8-20), and 79% of all PMAs approved during our study period were the subject of at least one supplement in 2012. Over one-third (37%) of approved supplements involved a change to the device’s design. Among major design change supplements approved from 2010-2012, 23% included new clinical data to support safety and effectiveness.

Many of the pacemaker, implantable cardioverter-defibrillator, and cardiac resynchronization therapy models currently used by clinicians were approved via the PMA supplement process, not as original PMAs. The supplement process facilitates incremental device innovation, providing an efficient and inexpensive review pathway for smaller device changes. Most new CIED models are deemed safe and effective without requiring new clinical data reinforcing the importance of rigorous post-approval surveillance of these devices.
Task Specific Fatigue Among Older Primary Care Patients

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Fatigue is a common condition linked with mobility decline and disability among older patients. The purpose of this study was to determine if self-reported task-specific fatigue was associated with corresponding task performance among community-dwelling primary care patients.

Participants included 430 primary care patients ≥65 years old from the Boston area taking part in the Boston Rehabilitative Impairment Study of the Elderly. Baseline data, collected from 2009 to 2012, was utilized for this analysis. Fatigue was measured using the Avlund Mobility-Tiredness Scale. Performance tasks were measured using the chair stand time and 4-meter walk test of the Short Physical Performance Battery as well as the stair climb time of the Stair Climb Power Test. Additionally, we collected data on age, gender, BMI, education, number of co-morbidities, physical activity, depressive symptoms, cognitive status, pain, and leg strength.

Among the participants, 15%, 16%, and 50% were fatigued while rising from a chair, walking indoors, or climbing stairs, respectively. Pain was the only attribute that was consistently predictive of fatigue status, although number of co-morbidities and leg strength were predictive of two of the three tasks. Both chair rise fatigue and walking fatigue were significantly associated with task performance. Stair climb fatigue was not associated with stair climb time.

In conclusion, pain was consistently associated with fatigue while rising from a chair, walking indoors, or climbing stairs. While further research is needed, this study supports the validity of self-reported chair rise fatigue and walking fatigue as individual test items.
Molecular Recognition Properties of Olfactory TAARs

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Olfaction is a critical modality for the generation of perception and the regulation of innate behaviors in mammals. This system is mediated by sensory neurons (SNs) located in the olfactory epithelium, with rodents also having SNs in the vomero nasal organ. Each SN expresses a receptor that belongs to one of two G-protein coupled receptor (GPCR) families: the canonical odorant receptor (ORs) family or the trace amine-associated receptor family (TAARs). Odorant receptors represent the largest gene family in mammals; in direct contrast, TAARs comprise a much smaller gene family that is more closely related to biogenic amine receptors. Ligands have been recently discovered for many of these TAARs, all of which are primary and tertiary amines. One such ligand found in carnivore urine has been recently shown to trigger aversion in rodents (Ferrero, Liberles, et al 2011). A second ligand has been found to be sexually dimorphic in mouse urine and is believed to be linked to pheromone signaling (Liberles & Buck 2006). Despite advances in understanding the physiological function of some receptors, the principles governing the ligand binding and specificity remain undefined. This study aims to address this aspect of TAAR signaling.

The homology between a cluster of five TAARs (mT7 a-f) combined with acute differences in ligand affinity allow for a focused identification of ligand contact sites. Amino acids responsible for receptor identity and ligand affinity are likely located in the transmembrane (TM) and extracellular regions with an emphasis on the region surrounding an aspartic acid of TM3 shown to be critical to biogenic amine function (Shi & Javitch 2002). Comparison of various TAARs using an alignment algorithm allowed us to eliminate stretched of conserved sequence and focus on areas of variation. Our analysis indicated 2 putative critical residues located in close proximity to the aspartic acid of TM3 to be significant.

In order to test the significance of these 2 residues, we chose to mutate them using overlap extension polymerase chain reaction (PCR). First, the protein was isolated from mouse olfactory epithelium tissue. We then introduced our mutations and ligated the products into a mammalian expression vectors. These new mutant receptors were then tested using a functional assay for GPCRs. The resulting dose response curves were used to infer the affinity of our receptors to our particular ligands.

In this study, mutant mTAAR7 receptors were generated and their response profiles were compared to those of the wild type receptors. In preliminary data we show that removing the polar side chains from two residues in the TM3 region via mutation to alanine caused a marked decrease in ligand specificity. Furthermore, swapping these two residues between mT7e and mT7f alters response profiles to resemble the opposite receptor. This suggests that they are largely responsible for ligand specificity and conferring receptor identity. GPCRs are the largest family of TM receptors, and critical targets for therapeutic drug development. These findings help define the basis for TAAR ligand binding and specificity which may be applicable to other GPCRs.

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An Economic Comparison of Internal vs. External Clinical Trial Initiation at Montefiore Medical Center, Bronx, NY as part of the Harvard MD/MBA Program

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At Montefiore Medical Center and the Albert Einstein College of Medicine, industry sponsored clinical trials can be initiated through either an internal or external pathway. The internal pathway involves the personnel of the Office of Clinical Trials (OCT) of Montefiore/Einstein, while the external pathway uses a Clinical Research Organization (a CRO), called BRANY, which Montefiore partially owns. Clinical trial initiation depends on budget negotiations, contract negotiations, startup logistics, patient and PI recruitment, and subsequent trial management and invoicing. Furthermore, BRANY and the OCT have different pay scales and infrastructure for running the trials.

Members of both the OCT and BRANY were interviewed to obtain data on budget turnaround times, contract negotiation times, and startup management. In addition, a full data set of 2012’s clinical trials was analyzed. Revenue was broken down into both its source (an OCT or a BRANY trial), as well as the area it came in from: Direct Patient Related Research Costs, Overhead, IRB fees, OCT Admin Fees, BRANY Admin Fees, and Indirect Costs.

Using the 2012 data, scenarios were then generated regarding the potential loss or gain of revenue through different allocations of industry clinical trials and their assigned place of management – internally or externally. The data was further broken down into a division of labor among the pathways, e.g. running the trial internally but using an external IRB etc. Ultimately a proposal was generated of the most cost efficient allocation of clinical trial initiation, which is now in the early stages of implementation at Montefiore Medical Center.

The recommended allocation serves to increase revenue to OCT and further support BRANY in its mission, while also creating a significantly more efficient allocation of personnel to the management of trials that are activated, and direct support to PIs and their research staffs. This recommendation frees up internal staff to direct attention to recruitment, retention of subjects, and affords both parties – OCT and BRANY – additional revenue.
Assessing the use of interactive voice response technology in a smoking cessation intervention

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Smoking is the leading preventable cause of death in America. Each year 4 million smokers are hospitalized, providing clinicians an opportunity to intervene. Hospital-initiated smoking cessation programs are effective when paired with post-discharge follow-up, yet are not widely adopted in U.S. hospitals. A scalable, cost-effective model for delivering tobacco treatment after discharge is needed. This project used automated telephone technology with interactive voice response (IVR) to deliver free smoking cessation counseling and medication to patients post-discharge. Our goal was to assess the utilization of, satisfaction with, and dose-response effect of an IVR-based smoking cessation program among hospitalized smokers.

We analyzed data from 197 subjects randomized to the intervention arm (IA) of Helping Hand, an RCT conducted at MGH (2010-2012) that enrolled 397 patients who were > 18 yrs old, daily smokers, and planning to quit once discharged. IA subjects received a 1-month supply of stop smoking meds (refillable x2) and 5 IVR calls that offered counseling and med refills. Outcomes were assessed at 1, 3, and 6 months post-discharge. We measured the proportion of IVR calls completed, services requested, and patient-reported satisfaction. To evaluate impact, we ran logistic regressions on 7-day smoking abstinence at 6 months post-discharge, with the number of IVR calls completed as the predictor of interest.

Sixty-four percent of 990 potential IVR calls were completed and >50% of subjects completed 4+ (>80%) calls. Males (p=0.03) and older patients (p=0.04) completed more calls. Patients were more likely to use IVR calls to request med refills (72%) than counseling (37%), although women were more receptive to counseling than men (45% v. 30%). Seventy-five percent of patients found IVR calls useful. Each additional IVR call completed was associated with a 1.38-fold increase (95%CI: 1.09-1.74) in the odds of 7-day abstinence at 6 month follow-up, after controlling for sex, age, and education.

The original study design did not allow us to isolate the effect of IVR from access to free meds on quit rates. We could only analyze data from IA subjects, so sample size limited our statistical power to detect differences in outcomes. Nevertheless, many of our findings were statistically and substantively significant.

Using IVR to deliver smoking cessation programs after hospital discharge is feasible and acceptable to a broad range of patients, and appears to improve smoking cessation rates. Moreover, IVR offers a potentially cost-effective way to deliver tobacco treatment routinely and systematically to hospitalized smokers.
A Patient-Centered, Electronic Care Planning Tool that Facilitates Team-Based Care and Patient Engagement

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Team-based care (TBC) and patient engagement are central components of the patient-centered medical home (PCMH). However, there are presently no adequate information technology (IT) solutions to support the communication and coordination central to TBC, and patient engagement is difficult to achieve without eliciting patients’ goals. We hypothesized that a novel, shared, electronic care plan (CP) tool that incorporated patient-generated goals could address these needs.

Our intervention took place at the Phyllis Jen Center (PJC), an Internal Medicine teaching practice that provides primary care to 20,000 patients, many of whom are medically and socially complex. We conducted structured observations and interviews with PJC staff to inform the development of an electronic CP tool that could be embedded within existing IT systems. We also conducted patient interviews to inform the design of a picture-based goal-setting document that would help patients generate their own goals for inclusion in CPs. We then piloted use of a simulated version of an electronic CP tool for high-risk diabetic patients on one PJC clinical team, and tested a picture-based goal-setting document with multiple providers’ diabetic patients. Care team members, providers, and patients were interviewed upon completion of pilots.

In baseline interviews, we found that care team members prioritized a CP’s ability to provide a real-time summary of a patient’s comprehensive care needs, display a patient’s most pertinent background information, facilitate within-team task assignment, and help organize tasks. In the pilot, use of a CP platform improved team members’ ability to see what their colleagues were doing for a patient, access background information for patients, assign tasks within the care team, and keep track of their own tasks. Use of a picture-based diabetes goal-setting document helped patients reflect on their self-care and increased follow-up with diabetes-related referrals. Providers noted that use of this tool during visits gave them new insight into patients’ needs and allowed them to base discussions on patients’ self-care goals.

Our work demonstrates that an electronic CP tool can enhance within-team communication, coordination, and information sharing, and that use of a picture-based goal-setting document boosts patient engagement in diabetes care. A platform that combines both aspects of our work will be invaluable for facilitating TBC, patient engagement, and management of complex patients in the PCMH. Next steps include integrating our CP and goal-setting tools and embedding the CP tool within existing IT systems. Limitations include the limited size and scope of pilots conducted thus far.
Improving Transitions of Care: Understanding Hospital Utilization at BWH
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Readmissions not only represent a great cost to the healthcare system, but may reflect inadequate care or unresolved social needs. The Patient Centered Medical Home (PCMH) is uniquely designed to address such needs, and thereby reduce hospital utilization. Brigham and Women’s Advanced Primary Care Associates, South Huntington (SH) is a PCMH committed to data-driven quality improvement. We sought to evaluate the efficacy of the PCMH model, and specific SH interventions, in affecting readmissions by measuring rates and trends of hospital utilization among SH patients.

Interventions were aimed to meet the needs of patients at risk for hospitalization. They included the general team-based PCMH structure as well as a Transitions Team composed of the patient’s primary providers plus members of a team of shared resources. Central to this team were the Care Coordination Nurse (CCRN) responsible for inpatient, outpatient, and home-care coordination, Population Manager to identify high-need patients for patient care teams, and medical students responsible for data collection and analysis.

Efforts to improve care transitions also included several specific innovations:
(1) An At-Risk Patient Registry is managed by the CCRN with all relevant information to track patient admissions, readmissions, and ED visits. (2) In Population Huddles, teams regularly meet to discuss high-risk patients identified by the Population Manager, and determine roles and tasks for outreach. (3) The Post-discharge Checklist, based on a post-discharge process map, is designed to remind providers of key questions and tasks to prevent readmissions. (4) The Post-discharge Visit is scheduled by the CCRN who talks with patients during and after admission; the highest-risk are seen within 72 hours and all others within 1-2 weeks. Visits include patients’ PCP, pharmacist, and CCRN.

We tracked rates of monthly hospital utilization among SH patients using both hospital and clinic-based information systems between September 2011 and June 2013. We then completed chart reviews for patients readmitted between January 2013 and July 2013 using the previously-validated HOMERUN Readmission Care Audit.

Overall, hospital utilization among SH patients decreased between September 2011 and April 2013. Rates of admission and ED visits fell from 14/1,000 to 7/1,000 and 31/1,000 to 24/1,000, respectively. Interestingly, traditionally-calculated rates of readmission (readmission rates/admission rates) appeared unchanged. Against a background of declining admissions (a decreasing denominator), this calculation failed to capture changes in readmissions. Calculated instead as a raw fraction (absolute readmissions/1,000 patients), we found readmissions declined from 3/1,000 to 1/1,000, despite falling admissions.
Complete genome sequencing of *P. gingivalis* isolated from rheumatoid arthritis patients

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*Porphyromonas gingivalis*, an oral anaerobe and one of the major bacterial pathogens implicated in adult periodontitis, has also been associated with rheumatoid arthritis (RA). Previous studies have demonstrated that RA is more prevalent in periodontitis patients than in the general population, and considerable research has been devoted to understand the causative link between the two diseases. One of the key characteristics of RA is autoimmunity to citrullinated proteins. Citrullination is a post-translational modification involving the conversion of peptidylarginine to peptidylcitrulline by a family of calcium-dependent peptidylarginine deiminases (PADs). *P. gingivalis* is the only bacterium known to express a PAD enzyme and thus is thought to enhance the autoimmune process in a subset of RA patients.

Based on the putative association between *P. gingivalis* and rheumatoid arthritis, we sought to sequence the genome of *P. gingivalis* isolated from RA patients and to align these sequences against previously published genomic sequences of two *P. gingivalis* laboratory strains, W83 and ATCC 33277. We hypothesized that more genetic variation at the nucleotide level would be present in *P. gingivalis* isolated from RA patients compared to W83 and ATCC 33277. To test this hypothesis, we obtained gingival crevicular fluid samples from early rheumatoid arthritis patients at Massachusetts General Hospital who were subsequently referred to The Forsyth Institute for dental evaluation. All study participants had early RA symptoms for no more than one year and were not taking RA medications during the time of the study. Each gingival crevicular fluid sample was plated on blood agar to select for greyish-black colonies that are characteristic for *P. gingivalis*. Next, we isolated chromosomal DNA from bacterial colonies using a DNA purification kit. We used *P. gingivalis* specific 16S rRNA primers in a PCR reaction to confirm presence of *P. gingivalis* in our clinical samples. Finally, we plan to use the Illumina MiSeq Personal Sequencer to sequence the recovered DNA and align this sequence against the known genome sequences of W83 and ATCC 33277.

To date, results from PCR have confirmed the presence of *P. gingivalis* in gingival crevicular fluid samples from nine patients enrolled in the study. A major limitation in completing this project on time was the fact that the bacterial incubation period was longer than expected. Another limiting factor is the presence of other black-pigmented anaerobes in samples (i.e. Prevotella species).
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Evaluating General Dental Practitioners’ Willingness to Assume Greater Responsibilities in Providing Limited Preventive Primary Care

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The United States is in need of greater access to primary care at lower cost. The dental workforce is a previously untapped resource of healthcare professionals capable of providing limited primary care services. If dentists, who are already de facto oral physicians, could become providers of basic services that lead to prevention and/or monitoring of costly chronic diseases such as hypertension, diabetes, in addition to detection of developmental disorders, substance and domestic abuse, administering vaccines, monitoring compliance with prescribed medications, which could translate to huge costs savings. To develop and implement these programs will require a continued commitment among a significant proportion of current and future dentists. However, even with possible liability for not being aware of underlying medical issues in their patients, many independent dentists may be unwilling to assume the additional responsibilities and training to provide primary healthcare services. The purpose of this study is to determine the willingness, through surveys, of general dentists to seek additional training to provide limited aspects of primary healthcare. Questions are designed to elicit the length, type, and aspects of training that general dentists would be willing to assume.

The survey is currently undergoing pretesting for validity, relevance, clarity, inclusiveness, and reliability or topics ultimately selected for the final survey to be administered to probability samples of dentists in general practice and/or specialty training. For example, there is great confusion over the proposed change in professional title to “oral physician,” which despite its status of being a dentist, is the most accurate term to describe the scope of what dentists can and should provide, including limited preventive primary healthcare.

The number of surveys to be distributed by e-mail will depend on the estimated return rate for surveys sent to groups of dentists who will be randomly and proportionately sampled from general practitioners and those in specialty training from a marketing database (Dentist List Pro) obtained from yellow and white pages directories, county courthouse and secretary of state data, annual reports business directories, internet search engines, SEC filings, new business registration and incorporations, and postal service information.
Sex Differences in Bone Loss with Weight Loss in the Pounds Lost Trial: Evaluation of Mechanisms

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Obesity is an increasingly prevalent health concern, and according to the CDC, over 2/3 of Americans are overweight or obese. Weight loss can be helpful for preventing medical complications of obesity, but it is important to understand potential sequelae of weight loss when treating overweight patients. Loss of bone mass is a known complication of weight loss and increases patients’ risk of osteoporosis and fracture. Minimizing bone loss should thus be a goal of weight loss treatment. In the POUNDS LOST trial, 811 obese and overweight individuals were randomized to 1 of 4 diets varying in macronutrient content and followed for two years. While participants lost similar amounts of weight across the four diets, women lost BMD at the spine (LS) and femoral neck (FN) while men gained BMD at the LS. The purpose of this study was to understand mechanisms by which women lost BMD with weight loss and men did not.

In 231 POUNDS LOST participants we analyzed biomarkers of bone turnover (osteocalcin, C-telopeptide), adipokines (leptin, adiponectin), and calcium homeostasis (calcium, 25-OH Vitamin D, PTH) at baseline and after 2 years of weight loss. Multivariate analyses correlated the 2-year changes in these biomarkers with changes in LS and FN BMD.

At the LS, C-telopeptide was inversely related to BMD loss in women ($r=-0.41$) but directly related to BMD gain in men ($r=0.03$; sex difference $p<0.001$). Men showed a negative relationship between leptin and LS BMD ($r=-0.19$) and at the FN ($r=-0.03$); women showed a direct relationship between leptin and LS BMD ($r=0.1$) and a similar trend at the FN ($r=0.2$; sex difference $p=0.027$ at the LS and $p=0.06$ at the FN). Vitamin D was positively correlated with BMD in women at the FN ($r=0.28$) but negatively correlated with BMD changes in men ($r=-0.08$ at the FN, sex difference $p=0.006$).

These results suggest that with weight loss, there are sex differences in the relationship between changes in leptin, bone turnover, and vitamin D and changes in BMD. Bone breakdown increased in women, but not in men. As leptin decreased, BMD decreased in women but increased in men. Vitamin D appeared to protect women from BMD loss. Since osteoporosis affects one of every two American women but only one of every four American men, understanding changes in biomarkers associated with weight loss may be useful for developing strategies to maintain bone health.
Are panoramic radiographs predictive of temporomandibular joint synovitis in children with juvenile idiopathic arthritis?

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Juvenile idiopathic arthritis (JIA) is a diagnosis of exclusion made in children 16 years of age or younger with a history of arthritis for at least 6 weeks. The temporomandibular joint (TMJ) is involved in more than 40% of children diagnosed with JIA. Sequelae of TMJ arthritis include restricted mandibular growth, malocclusion, and limited mouth opening.

The “gold standard” for diagnosis of active TMJ synovitis is joint tissue enhancement on magnetic resonance imaging (MRI) with gadopentetate dimeglumine. However, MRI has limitations: sedation, intravenous access, cost, and availability. As panoramic films are often obtained during routine dental care, it would be useful to determine which specific panoramic features are indicative of TMJ synovitis.

This was a retrospective study of children with JIA evaluated at Boston Children’s Hospital. Patients were included if they had a confirmed diagnosis of JIA and a TMJ MRI study with contrast and panoramic radiograph within a six month interval. Medical records and imaging studies were reviewed to document demographic, panoramic (accentuated antegonial notch, abnormal condyle morphology, short ramus/condyle unit (RCU) length, decreased condyle dimensions), and MRI findings. Outcome variable was TMJ synovitis on MRI. Descriptive and bivariate statistics and logistic regression models were used to identify associations (p-value <.05 significance).

Thirty patients (21 females) with a mean age of 11.1 years (range 5-16) met inclusion criteria. 15 subjects had MRI scans positive for synovitis: bilateral, 9 patients (18 joints) and unilateral, 6 patients (6 joints). The remaining 15 subjects did not have evidence of synovitis on MRI. In the synovitis group, 13 subjects had abnormal panoramic findings: abnormal condyle morphology (13 patients, 18 joints), accentuated antegonial notch (7 patients, 9 joints), and short RCU length (5 patients, 5 joints). In the non-synovitis group, abnormal panoramic findings included: abnormal condyle morphology (9 patients, 12 joints), accentuated antegonial notch (5 patients, 6 joints) and short RCU length (4 patients, 4 joints).

Abnormal condyle morphology and accentuated antegonial notching on panoramic radiograph were significantly correlated with synovitis (p=.0005 and .044, respectively). In a logistic regression model, abnormal condyle morphology was significantly associated with an increase in likelihood of TMJ synovitis (p=.007). Joints with abnormal condyle morphology and accentuated antegonial notching were 7.5 times as likely to have synovitis (p=.009).

Results of this preliminary study indicate in this sample of children with JIA, abnormal condyle morphology and accentuated antegonial notching on a panoramic radiograph correlate with TMJ synovitis on MRI.
Lack of dental insurance is correlated with edentulism among patients at a dental franchise in central Massachusetts

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The correlation between insurance status and edentulism has not previously been reported in a population with known access to a dentist, and little is known about patient demographics in corporate dental settings. This study investigated patient demographics of a former dental franchise in Chicopee, Massachusetts, and examined a correlation between dental insurance and edentulism in this group. The correlation of edentulism with age, gender, and dental risk factors (diabetes, temporomandibular disorder, trouble with previous dental work, or oral sores and ulcers), was also examined.

This was a retrospective case study. Age, gender, and presence of dental risk factors were recorded from the patient medical history intake form. Dentate status was recorded from patient odontograms. Dental insurance status was obtained from billing records. Data were aggregated and deidentified. Descriptive and bivariate statistics and logistic regression models were used to identify associations (p-value ≤ .05 significance).

Of 1,123 records meeting inclusion criteria, 52.54% of patients had dental insurance, 26.27% had at least one dental risk factor, and 18.17% were edentulous. Age and insurance status were significantly correlated with edentulism. Correcting for age, individuals without insurance were 1.56 times as likely to be edentulous.

This case study provides insight into patient demographics that might seek care in a corporate setting and suggest access to a dentist alone may not be adequate in preserving the adult dentition; dental insurance may also be important to health. As the corporate dental practice model continues to grow, these topics deserve further study.
Incorporating Reproductive Health Care into the Patient-Centered Medical Home
at Brookside Community Health Center

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For women of reproductive age, access to comprehensive, quality pre-conception care and family planning is essential to achieve planned and well-timed pregnancies, as well as to reduce adverse pregnancy complications and sexually transmitted infections, all of which have substantial effects on the health of women and children. With the implementation of the Affordable Care Act, our nation is incorporating patient-centered medical homes into our national health care agenda. However, there has been minimal discussion about how to effectively implement reproductive health care – specifically pre-conception care and family planning – into the patient-centered medical home.

Based on previous research highlighting the missed opportunity to deliver reproductive health care during a primary care visit with a negative pregnancy test, the goal of this quality improvement project was to identify the reproductive health needs of young women and to explore ways effective care delivery can be incorporated into the patient-centered medical home at Brookside Community Health Center in Jamaica Plain, Boston. The objectives were to identify the reproductive health needs of low-income women of reproductive age, including barriers to pre-conception care and family planning; to delineate the reproductive health care best practices in a patient-centered medical home, including the specific strengths and areas for improvement at Brookside; and to design an effective and sustainable intervention to enhance reproductive health care delivery at Brookside.

Data was collected through semi-structured, open-ended interviews with Brookside staff – including medical providers, medical assistants, licensed practical nurses, family planning counselors, and secretaries – as well as patients who are women of reproductive age (18-44 years). The goal of these interviews was to identify, from both the patient and provider perspective, what constitutes optimal reproductive health care and current barriers to such care, as well as the strengths and areas for improvement of preconception care and family planning at Brookside. Interview summaries will be reviewed to identify themes.

From the data analyzed at this stage, it is apparent that both providers and patients believe reproductive health care solidly belongs within primary care. Identified barriers to such incorporation include patient access to resources (providers, educational material, and birth control), staff awareness and training about reproductive health care (especially for MAs and LPNs), and care coordination. Proposed solutions to these challenges include improved patient access and education, optimal training and utilization of providers, team-based care, population management and patient outreach. These solutions highlight major areas of focus of the patient-centered medical home applied to reproductive health care.
Systematic review of the manifestations of Congenital Rubella Syndrome

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Congenital rubella syndrome (CRS) continues to cause disability among unvaccinated populations, particularly in the 62 countries yet to introduce rubella vaccine and in immunized populations with insufficient vaccine coverage to prevent transmission. We systematically reviewed the literature on birth outcomes associated with CRS to estimate the duration, severity, and frequency of combinations of morbidities. We searched PubMed, the Science Citation Index, and references from relevant articles for studies in English with primary data on the frequency of CRS manifestations for ≥20 cases and identified 65 studies representing 66 study populations that met our inclusion criteria. We abstracted available data on CRS cases with one or more hearing, heart, and/or eye defects following maternal rubella infection during the period of 0-20 weeks since the last menstrual period. We assessed the quality and weight of the available evidence using a modified GRADE approach. Most of the evidence originates from studies in developed countries of cohorts of infants identified with CRS in the 1960s and 1970s, prior to the development of standardized definitions for CRS and widespread use of vaccine. We developed estimates of undiscounted disability-adjusted life-years (DALYs) lost per CRS case for countries of different income levels. The estimates ranged from approximately 28 to 40 for high-income countries assuming optimal treatment and approximately 32 to 42 DALYs lost per CRS case in low- and lower middle-income countries assuming minimal treatment, with the lower bound based on 2010 general global burden of disease disability weights and the upper bound based on 1990 age-specific and treatment-specific global burden of disease disability weights.
Exploiting mutation data to intelligently target the mTOR pathway for cancer therapy with Rapamycin and ATP competitive inhibitors

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The abundance of human cancers associated with mutations in the PI3K/Akt pathway makes it an excellent candidate for the study of the genetic basis of cancer and the search for novel therapeutic agents. One known downstream effector protein of PI3K is the mechanistic Target of Rapamycin (mTOR) protein.

The mTOR protein is a pivotal regulator of cell growth and division and so hyper-activation of mTOR has been associated with many known cancer types. Involvement of mTOR in the development of cancer has led to the hypothesis that Rapamycin, an allosteric inhibitor of mTOR, can be used to treat PI3K/Akt/mTOR related cancers. We are tantalizingly close to using currently approved drugs like Rapamycin for effective treatment of PI3K/Akt/mTOR related cancers, yet associated clinical trials proved the drug was not as effective as had been projected. It is possible that a smaller subset of mTOR related cancers are susceptible to Rapamycin rather than all. Characterization of mTOR mutations could allow us to better predict their sensitivity to Rapamycin.

Relevant oncogenic mutations were identified by looking for mutations that recurred in cancer cell lines using data collected from patients and cancer databases. Recurrent mutations in other pathway proteins such as NPRL2, Akt, and RICTOR were also included. Recurrent mutations were tested in 293T cells for hyper-phosphorylation of the downstream protein S6K. From these tests, we were able to identify several oncogenic mutations in the PI3K/Akt/mTOR pathway proteins that may be amenable to Rapamycin treatment.

To better understand how these mutations may cause cancer, mutations were mapped to the known domains of mTOR and onto the recently solved crystal structure of the protein. Ongoing experiments on how mutant proteins localize within the cell in response to activating signals will further help us understand the mechanism of activation in mutant lines. Since mTOR activation requires localization to the lysosome, fluorescent microscopy will be used to assess whether mutant proteins are still able to co-localize.

Finally, 293T cell lines with stable expression of oncogenic mutations were generated. These cell lines will be used to test Rapamycin sensitivity of the oncogenic mutations. If effective, mouse models will be developed to further investigate the efficacy of treatment. Ultimately, with the information on oncogenic mutations mechanisms and sensitivity to drugs we currently use to inhibit the pathway, we hope to be able to better screen patients who are could candidates for mTOR inhibition therapy.
Effect of Massachusetts Health Reform on Insurance Gaps, Access, and Financial Protection for Children with Special Health Care Needs

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Background and Objectives: Children with special health care needs (CSHCN) face unique challenges in accessing affordable health care. Massachusetts (MA) implemented a major health reform in 2006; little is known about the impact of MA health reform on gaps in insurance coverage, access to care, and financial protection for privately and publicly-insured CSHCN.

Methods: We used a difference-in-differences (DD) approach to compare gaps in insurance, access to care, and financial protection in MA versus non-MA states pre and post-MA health reform. We used parent-reported data from the 2005/2006 and 2009/2010 National Survey of Children with Special Health Care Needs and adjusted for age, sex, race/ethnicity, number of functional difficulties per child, and non-English language at home.

Results: Post-reform, living in MA was not associated with significant decreases in insurance gaps or increases in access to primary care for CSHCN. For privately-insured CSHCN, MA was associated with increased access to specialty doctors (DD=6.0%; p=<0.001). For publicly-insured children, however, MA was associated with a significant decrease in access to prescription medications (DD= -7.2%; p=0.003). Living in MA post-reform was not associated with significant changes in financial protection for privately or publicly-insured CSHCN.

Conclusion: MA health reform likely improved access to specialty care for privately-insured CSHCN, but did not decrease insurance gaps, increase access to primary care, or improve financial protection for CSHCN generally. Comparable provisions within the Affordable Care Act may produce similar outcomes; CSHCN-specific policies may be necessary to reduce gaps in insurance and improve financial protection.
Missed Opportunities Training Third Year Medical Students to Care for Seriously Ill Patients

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Medical students have few clinical experiences caring for seriously ill and dying patients during required clerkships. When students are able to participate in caring for these patients, they often experience existential distress and do not receive adequate feedback from their teams. Prior studies have underestimated the extent of opportunities to train medical students in palliative care competencies during their core clinical clerkships.

The purpose of this study was to identify missed opportunities training third year medical students during core clinical clerkships by describing and quantifying students’ experiences caring for seriously ill patients, evaluations of these experiences, and attitudes toward providing this type of care.

All 157 third year medical students at Harvard Medical School during the 2012-2013 academic year were invited to complete either an electronic or paper survey during the last four months of their third year. Surveys investigated medical students’ experiences, evaluations of their experiences, and attitudes towards caring for seriously ill and dying patients.

Eighty-eight students responded (RR=56%). Nearly all respondents (93%) felt that it was “moderately” or “very” important to learn about caring for seriously ill and dying patients. Students cared for a median of 1 patient who died, with 26% never caring for a patient who died. Over half (55%) never delivered significant bad news to a patient, and 38% never worked with a specialist in palliative medicine. Eighty-four percent of students who cared for a dying patient and 60% of students who delivered significant bad news had one of more experiences that were not debriefed with their team. 31% of students gave bad news to a patient without supervision.

We conclude that when third year medical students have an opportunity to care for a seriously ill or dying patient during required clerkships, faculty may miss opportunities to teach essential medical student palliative care competencies. Both palliative care consultants and clerkship faculty should identify opportunities to supervise and debrief these experiences with the students.
The Serious Illness Communication Checklist: Expanding a Randomized Controlled Trial to a Primary Care Setting

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Primary care providers (PCPs) have a critical role in ensuring that patients receive the type of care they want at the end of life. However, competing demands undermine PCPs’ ability to conduct advance care planning (ACP) conversations that equip them to advocate for their patients’ wishes. Such time constraints, coupled with the average PCP only having 3 to 5 patients who die each year, make identifying the ‘right’ patient with whom to have an ACP conversation challenging. To address these challenges, we have developed a Serious Illness Communication Checklist (SICC) intervention that aims to provide PCPs at Atrius Health/Harvard Vanguard Medical Associates (HVMA) with an evidence-based method for identifying “high risk” patients and eliciting and documenting their goals and wishes about their end-of-life care.

In the context of a cluster randomized controlled trial, we aim to: 1) assess the feasibility of using risk stratification algorithms to identify appropriate primary care patients for ACP conversations, 2) determine the acceptability of the SICC intervention among patients and clinicians, 3) examine the impact of the SICC on patients’ quality of life and receipt of goal-consistent care, and 4) investigate the effects of the SICC on resource utilization in a closed payer/provider primary care organization.

Based on preliminary data from Dana Farber Cancer Institute, implementation of the SICC is feasible and acceptable to patients and clinicians, with 95% of clinicians planning to continue using the conversation guide upon study completion. Physicians report conversations taking an average of 20 minutes, suggesting that such conversations are practical in the primary care setting.

An innovative collaboration with Atrius Health/HVMA has extended the SICC intervention by using a risk stratification system to identify appropriate primary care patients for ACP conversations. This risk score identifies “very high” risk patients who have a 35% 6-month mortality rate; thus, identifying patients most likely to benefit from ACP conversations. Using combined clinical and administrative data from Atrius/HVMA as a closed payer/provider organization will allow a comprehensive analysis of health care utilization and costs.

From our collaboration we have learned that risk stratification algorithms can identify “high risk” patients who are most appropriate for and will likely benefit the most from ACP conversations, maximizing the benefits of invested resources. Primary care practices can and are willing to pilot, and spread, initiatives developed in a research environment.
Moderate Alcohol Consumption is Associated with Lower Levels of Myocyte Injury and Myocyte Stress in Healthy Women

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Background: Alcohol use, cigarette smoking, physical activity, and fruit and vegetable consumption are modifiable cardiovascular risk factors that have a substantial impact on the risk of myocardial infarction, stroke, and cardiovascular death. However, the biologic mechanisms by which these factors modify cardiovascular risk are not well understood. We hypothesized that these behaviors may alter circulating concentrations of cardiac troponin T (cTnT) and B-type natriuretic peptide, which are markers of myocyte injury and stress that have shown strong association with adverse cardiovascular outcomes.

Methods: In 564 women with no evidence of cardiovascular disease, we used a novel, high sensitivity assay to measure circulating concentrations of cTnT, and a commercially available assay to measure the amino-terminal fragment of B-type natriuretic peptide (NT-proBNP). We tested for association between alcohol use, cigarette smoking, physical activity, and fruit and vegetable consumption and circulating natural logarithm-transformed NT-proBNP using linear regression. We used logistic regression to determine if these behaviors were associated with detectable cTnT or with NT-proBNP in the highest quartile (≥117.4 pg/ml).

Results: The median (IQR) age of the cohort was 56.7 (50.9-64.3), and the median (IQR) NT-proBNP was 64.2 (37.8-117.4). 30.3% (171/564) of the cohort had detectable circulating cTnT. We observed no significant relationship between the modifiable cardiovascular risk factors, including alcoholic drinks per day (β: -.0059, SE: .0054, P=.28), and ln(NT-proBNP). However, in models adjusted for age, race, blood pressure, body mass index, high and low density lipoprotein, triglycerides, estimated glomerular filtration rate, and other behavioral risk factors including physical activity, cigarette smoking, and current hormone therapy use, women who drank 1-6 drinks per week were at lower risk of having either a detectable cardiac troponin (OR: 0.59, 95% CI: 0.35-0.93) or an elevated NT-proBNP (OR: 0.55, 95% CI: 0.32-0.95). Physical activity, cigarette smoking, and fruit and vegetable consumption were not associated with detectable cTnT or elevated NT-proBNP.

Conclusions: In our study, moderate alcohol consumption, but not other modifiable risk factors, was associated with a lower risk of having elevated NT-proBNP and detectable levels of cTnT. These results raise the possibility that the beneficial effects of moderate alcohol consumption on cardiovascular risk may be mediated by direct effects on the myocardium.
Physical Activity and Experience of Total Knee Arthroplasty in Patients 1-4 Years Post-surgery in the Dominican Republic: A Qualitative Study

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Musculoskeletal disorders including osteoarthritis (OA) are the second-leading cause of years lived with disability globally. For patients with advanced knee OA and concomitant disability, total knee arthroplasty (TKA) offers relief from pain and functional limitation and the opportunity to return to physical activity, which can enhance mental and physical health. Despite the increasing global burden of OA, there has been no published research on physical activity after TKA in the developing world.

We sought to understand the extent to which patients return to physical activity after TKA in a developing nation through qualitative interviews with 18 economically disadvantaged Dominican patients (78% women) who received TKA between 2009 and 2012 as part of the Operation Walk Boston surgical mission program. We classified physical activities as obligatory, committed, and discretionary. Obligatory activities are activities of daily living including walking for transportation, committed activities are associated with one’s principle productive social role, and discretionary activities include exercise and recreational activities. Interviews were conducted in Spanish, and English transcripts were analyzed using content analysis.

TKA affected the ability to perform at least one obligatory, committed or discretionary physical activity for all patients in the study. Many patients found that TKA increased their participation in several physical activities in different life domains such as occupational or social pursuits. Some patients appeared to limit their own physical activities due to misinterpretation of physician instructions or uncertainty about appropriate joint use. Many patients noted positive effects of TKA on mood and mental well-being, and every patient was satisfied with the impact of TKA on his or her life and would choose to have surgery again in hindsight. For most patients in the study, religion offered a framework for understanding their receipt of and experience with TKA.

Our findings underscore the potential of TKA to permit patients in the developing world to return to physical activities. This research highlights the need to develop, implement and evaluate interventions to improve physical activity following TKA in these settings. Our findings also demonstrate the importance of patient education, culture, and religion in patients’ return to physical activity following TKA. As the global burden of musculoskeletal disease increases, it is important to understand the impact of chronic arthritis on patients’ lives in the developing world and to optimize the potential for surgical intervention to improve quality of life and reduce years lived with disability.
Radioprotection of Bone Allograft using Vitamin E Derivatives

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Bone allografts are commonly used to repair fractures and to perform skeletal reconstruction due to illness, injury, or tumor removal. Terminal sterilization by chemicals or ionizing radiation is commonly used against viral and bacterial disease transmission, which is of concern especially for Hepatitis and HIV. However, radiation sterilization impairs the mechanical strength of bone, particularly the bending strength, work to fracture, and impact energy. This decrease is likely the cause of an increased incidence of fracture in irradiated bone allografts in clinical setting (39 vs. 18%).

We hypothesized that radioprotection of allograft bone could be achieved by infusing with the naturally occurring antioxidant vitamin E prior to irradiation to improve the fracture toughness, work to failure, and IZOD impact strength of irradiated bone. Vitamin E has been used successfully to stabilize total joint implants since 2007.

To test this hypothesis, we infused bone blocks from bovine tibia with vitamin E or its derivative prior to irradiation. Three different types of treatment were conducted on each set of bone: (1) no treatment, (2) irradiation only at 25 kGy, (3) infusion with vitamin E or a derivative followed by irradiation at 25 kGy.

Infusing bone with vitamin E prior to irradiation resulted in recovery of fracture toughness by 36% (95% CI: 23 -48 %), work to failure by 40 % (95% CI: 3.7 -77 %), and IZOD impact strength by 39 % (95% CI: 8.2%-69 %). Infusing bone with vitamin E derivative prior to irradiation resulted in fracture toughness recovery of 60 % (95% CI: 22-99 %), work to failure by 52 % (95% CI: 32-71 %), and IZOD impact strength by 91 % (95% CI: 66-100 %).

Our hypothesis that radioprotection of allograft bone could be achieved by infusing it with vitamin E tested positive. We showed that infusion by vitamin E or its derivative enabled significant recovery of these properties. Vitamin E-treated bone was found to protect collagen crosslinking, significantly preventing the disruption of collagen cross-linking by irradiation, which is thought to be the major mechanism behind the deterioration of the mechanical properties of bone allograft. Improving the mechanical properties of bone allograft may benefit the load-bearing capability of structural grafts commonly used in skeletal reconstruction due to tumor resection, spinal arthrodesis, skeletal defects, and wedges for foot and ankle correction as well as that of morselized grafts most commonly used in spinal fusion.
The Impact of Regionalized Interdisciplinary Care Teams on Resident Teaching

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The Accreditation Council for Graduate Medical Education has placed restrictions on resident duty hours twice since 2003, most recently in July, 2011, which has markedly changed the structure of resident workload. Compounding the complexity of these duty hour restrictions for residency training programs, the ACGME has identified that “For the resident, the essential learning activity is interaction with patients under the guidance and supervision of faculty members who give, value, context and meaning to those interactions.” The changes to resident duty hours along with the demand for providing high yield resident teaching activities creates difficulty for all resident training programs trying to maximize resident exposure to patients while avoiding costly duty hour violations.

The general medicine service [GMS] at most academic teaching hospitals still operates with team structures and call cycles designed before the original ACGME duty hour restrictions, utilizing a four-day admitting cycle with a long-call, post-call, short-call, and pre-call day. This has resulted in a failure to evolve with the changing demands in resident workload structure, as evidenced by time-motion studies demonstrating a decrease in the proportion and total amount of time residents spend in educational activities and direct patient care since 2002. In addition, these outdated GMS structures lead to mismatches in workload supply and demand, inefficient care, decreased interdisciplinary communication, and interruptions in resident teaching. To date, no study has examined the effects of a GMS team structure redesign on resident teaching and patient care activities.

We hypothesize that a GMS with unit-based, interdisciplinary team structure and daily admitting will have improved resident workflow and increased educational opportunities including bedside teaching and team didactic sessions. To test this hypothesis, we are performing a pre/post time-motion analysis study of resident activities.

Time-motion observations were completed on eighteen resident day shifts before the GMS at Brigham and Women’s Hospital [BWH] switched form a four-day call cycle to unit-based, interdisciplinary teams with daily admitting in June of 2013. Residents’ activities were recorded in real-time by an observer using a database accessed remotely by iPAD. Analysis of the pre-implementation data showed BWH to be similar to other academic teaching hospitals with residents spending only 10.81 percent of time in direct patient care and 8.44 percent of time in learning activities.

In the spring of 2014, time-motion studies will be performed on 12 intern shifts and compared to our current data to measure the impact of GMS redesign on resident activities.
The Pioneer ACO Model – Lessons Learned from Flint, MI

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High health care costs and relatively low quality of care continue to be major issues in the United States. Many have pointed to physician incentives and payment structures as underlying causes of these problems. With the signing of the Patient Protection and Affordable Care Act (ACA) in 2010, the federal government put in place initiatives to address these issues. One such initiative was the creation of Medicare Accountable Care Organizations (ACOs). One particular type of Medicare ACO is the Pioneer ACO, which unlike the other ACO models outlined in the ACA, makes a systematic transition to a global payment strategy to incentivize health care provider organizations. Genesys Physician Hospital Organization (GPHO) is a newly formed Pioneer ACO in Flint, MI. Thirty-two Pioneer ACOs were selected in a highly competitive application process by the Center for Medicare and Medicaid Services Innovation (CMMI), and they began transitioning in January 2012. Although the Department of Health and Human Services is collecting data on the ability of this delivery model innovation to positively impact costs and quality, it is also important to document lessons learned and best practices from the various entities that participate in the initiative.

This study characterizes the major challenges in the first year of transition, as perceived by upper management and senior executives; the ways in which new incentives have affected upper management’s and physicians motivations toward cost saving; highlights some of the recent major innovations that are perceived to have improved patient value by reducing costs and improving patient outcomes; and provides a narrative of other lessons learned, major themes, priority setting considerations, effects of preparedness, and best ways forward for future small ACOs who serve urban communities.

We reviewed organizational historical documents (i.e. board and committee meeting minutes, balance sheets, etc.) to get an initial sense of the recent transition. We developed a questionnaire and interviewed 14 key GPHO executives in one-hour sessions. We also met with two groups of senior clinicians, one group of PCPs and one group of specialists, to develop physician questionnaires PCPs and specialists, respectively. The questionnaires have been sent out electronically to 160 PCPs and 400 specialists. Data from the physician questionnaires is in the process of being collected and will be analyzed. A report of overarching themes, interesting findings, specific lessons learned, and recent innovations will be drafted thereafter.
Personal Bias in Mental Health Expert Witnesses

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When a defendant is mentally ill, the court’s dual goals of protecting society and protecting the rights of the individual become even more difficult to attain. These complexities often necessitate the participation of a mental health expert in the trial—a participation limited in its effectiveness by the perception as well as the potential presence of bias. In order for mental health experts to serve the court system more effectively, we must improve our understanding of the drivers of expert witness bias.

Expert witness bias has typically been examined in terms of how its drivers affect professional behavior. Here, we seek to investigate how personal beliefs and experiences are included among those drivers. Beliefs about personal responsibility for mental illness have been shown to mediate bias toward the mentally ill in the public at large, and should be similarly relevant to an understanding of the attitudes and behaviors of mental health experts.

We surveyed mental health experts about their personal, nonprofessional exposure to persons with three forms of mental illness events (major depression, bipolar disorder, and schizophrenia). We assessed their beliefs about the role of mental illness in criminal behavior, as well as their beliefs about the responsibility of persons with mental illness for such illness, and sought to determine the extent to which these beliefs are correlated.
Development of a Clinically Relevant Orthotopic Model for Human Medullary Thyroid Cancer

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Background: Medullary thyroid cancer (MTC) accounts for approximately 5% of all thyroid cancers, and is derived from the parafollicular C cells. About a quarter of patients with MTC present with distant metastasis and these patients have worse survival rates, partially due to limited efficacy of postsurgical therapies. Factors hindering therapeutic development in MTC include the lack of a sophisticated preclinical animal model and few known targets for therapeutic agents. Orthotopic models provide an important tool for studying the progression and metastasis of cancer and are often used to test efficacy of novel drugs. Additionally, a cancer testis antigen and important immunogenic target in melanoma, NYESO-1, was previously found in MTC patient tissue samples. The overall goals of this study were to develop a clinically relevant orthotopic mouse model of human MTC and study the presence of NYESO-1 on the surface of MTC cell lines in vitro and in vivo utilizing the orthotopic model.

Methods: Two human MTC cell lines, TT and MZ-CRC-1, were cultured and tested for mRNA (RT-PCR) and protein expression (Western blotting) for NYESO-1, relative to expression in the control melanoma cell line, A375. The MTC cell lines were implanted orthotopically into the left thyroid of immunocompromised (SCID) mice: 3 mice with $1 \times 10^6$ TT cells and 5 mice with $2 \times 10^6$ MZ-CRC-1 cells. Mice were sacrificed up to 12 weeks post tumor implantation. Tumor volume was measured as $\pi/6 \times \text{length} \times \text{width} \times \text{height}$.

Results: Baseline NYESO-1 mRNA ratios were higher for TT (11 ± 0.24 fold) and MZ-CRC-1 (2.4 ± 0.08 fold), as compared to the control melanoma cell line, A375. Western blot analyses showed that both cell lines express NYESO-1 protein. There was no significant increase of NYESO-1 expression when the MTC cells were treated with DNA methylation inhibitor, deoxyazacytidine. Orthotopic tumors developed in many of the mice between 8-12 weeks post-implantation, 3/3 TT mice developed tumors, growing up to 35 mm$^3$. 4/5 MZ mice developed tumors, which grew up to 149 mm$^3$. No lymph node or lung metastases were visible grossly. Immunohistochemical staining showed significant expression of NYESO-1 in both TT and MZ orthotopic tumors.

Conclusions: We have successfully produced an orthotopic mouse model of primary MTC using both MZ and TT human medullary thyroid cancer cells. Histologic evaluation of the orthotopic tumor showed expression of NYESO-1, correlating with in vitro expression. This novel model could be useful for testing novel drug and vaccine-based immunotherapies in preclinical studies.
Improving attendance to primary care appointments: Randomized control trial of text messaging and additional reminder calls to high-risk patients at a community health center

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Poor adherence to medical appointments not only negatively impacts quality of care, but also reduces access to care for other patients. In 2012, the MGH Chelsea HealthCare Center Adult Medicine practice had the highest no-show rate (16%) in our hospital’s primary care network. A previous pilot study revealed that forgetfulness and miscommunication were the most common reasons for patient “no-show.”

To address this, we developed a randomized control trial (RCT) to evaluate interventions to improve appointment attendance rates. MGH Chelsea is a community health center serving predominantly Latino, non-English speaking, and low-income patients. All adult patients seen at the practice are eligible and are randomly assigned into one of the 3 arms: Control: Usual care (20%) receive a reminder phone call 2 days prior to appointment; Intervention 1: (60%) receive usual care and text message reminder 7-days and 1-day prior to appointment; Intervention 2: (20%) receive usual care and, if high-risk for no-show, an additional phone call 7-days prior to appointment. We designed an informatics tool to automatically provide Patient Services Coordinators (PSCs) with electronic rosters of patients who are due for a call reminder, and send text message reminders to patients prior to their appointments. Patients at high risk for no-show (as determined by a risk-predictive model) are flagged on the rosters.

The primary outcome is the no-show rate in the control and intervention groups. The secondary outcomes include: no-show rate by age, race, gender, language and insurance, by reminder call or text message outcomes in the three study arms, cancelled/rescheduled appointments, and return-on-investment. The mid-cycle data analysis is planned for October.

The RCT goes from 08/01/13-12/31/13. Patients were randomized, and PSCs are calling patients as indicated. The first text message to a patient was sent on 07/15/13. To date, 805 patients have been requested to enroll/consent via text message; 189 patients consented, and only 24 opted out. 592 patients did not respond after receiving the initial text and two subsequent reminders. Patient lack of access to mobile phones with SMS capability has resulted in lower enrollment in Intervention 2. We recently received IRB approval to enroll this subset of patients via phone.

Improving attendance to primary care appointments in underserved populations is challenging. Thus far, additional calls have generated more appointment cancelation, thereby improving access to care for other patients. At the end of five months, the study will show whether or not patients receiving text messages or additional reminder calls are more likely to attend their appointments.
EEG power differs by orders of magnitude between children and young adults under sevoflurane general anesthesia

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Evidence suggests that very young patients may experience adverse neurocognitive effects following general anesthesia (GA), but there is limited understanding about the fundamental brain mechanisms underlying anesthetic drugs, and standards of care for brain monitoring have yet to be established, especially in pediatric patients. To determine how sevoflurane, a commonly used GA drug in pediatric populations, affected brain function from childhood to young adulthood, we recorded 4-lead electroencephalogram (EEG) during routine care of patients receiving GA. We selected cases from two groups—children 0-17 years old (n = 17), and adults 18-35 years old (n = 11).

The EEG spectrum was estimated using the multitaper method over a 2-minute period of stable anesthetic maintenance. Average power in dB was calculated from the EEG spectrum of each patient in 6 canonical EEG frequency bands. We analyzed the relationship between EEG power and age in each of these frequency bands using a 4-parameter logistic model, which well-described the data. We also used a multitaper spectral comparison test to analyze the functional form of the spectrum, normalized for both cohorts. We identified a well-estimated sigmoidal relationship between EEG power and age, showing a rapid decline in power across all bands occurring between approximately 15-20 years old. This power decrease was 56-118 times larger in children than in young adults, depending on the frequency band. The EEG spectra appeared qualitatively similar in children and adults but showed differences in relative power within distinct bands.

Functional MRI studies suggest that cognition and cortical networks mature between approximately 15-22 years of age, paralleling a major phase in brain development where synapses are pruned by up to 50%. Thus, these age-related changes in sevoflurane-induced EEG oscillations may reflect systems-level neuronal changes that occur during development.

Our results may also explain why existing EEG-based anesthetic monitors are unable to accurately represent level of consciousness in children: they compute proprietary indices based on EEG power and ratios of EEG power, which are both significantly different in children compared to adults. However, since children and adults have qualitatively similar EEG spectra, it is likely that similar underlying neurophysiological principles apply, and a practical approach to future brain monitoring could entail identifying EEG spectral patterns associated with different anesthetic drugs. Furthermore, because anesthesia-induced EEG signals are so much larger in children, the problem of anesthetic brain monitoring may actually be easier to solve in children than in adults.
Comparison of robotic and manual needle-guide templates in MRI-guided transperineal prostate biopsy

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Purpose: To provide a comprehensive comparison of MRI-guided prostate core biopsy performed with a robotic device and with a manual template using 3T multiparametric MRI.

Materials and Methods: The study included 76 patients who underwent targeted transperineal prostate biopsy in wide-bore 3T MRI scanner. Patients were assigned to manual or robotic prostate biopsy based on the date of their procedure. Core biopsies were performed using a manual template and a robotic needle guide to collect core samples from tumor foci defined in MRI. Data recorded were: accuracy of needle placement, percentage of cancer volume in positive core samples and time to complete the procedure.

Results: 54 procedures were performed by manual template, and 25 procedures done using the robotic device. Average accuracy was 7.1mm in the manual group and 5.3mm in the robot group (P<.0024) An average of 43% of the submitted tissue returned positive for cancer in patients from the manual group, compared to 30% from the robotic group (P<.1672). The percentage cancer volume was higher in the manual group, although the difference was not statistically significant. The average procedure time for the manual group was 100 minutes, compared to 91 minutes for the robotic group (P<0.06). However, the average procedure time per sample was greater in the robotic group than the manual (P<0.0179).

Conclusion: The robotic device was safe and feasible in assisting in MRI-guided core biopsy of prostate cancer, yielding better needle placement accuracy than manual approach. Time to complete the procedures, diagnostic yield, and a volume of positive sample were comparable among both manual and robotic approach.
Improving photodynamic therapy response in a subcutaneous glioblastoma model

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One of the greatest current problems in cancer therapy is the lack of selective drug-targeting of tumor cells. More than 7 million people worldwide died from cancer in 2008 and the number is projected to increase to an estimated 13 million deaths by 2030. However, many current therapeutic options have severe side effects because they affect both normal and malignant tissue. One potential solution to overcome this limitation is photodynamic therapy (PDT). In PDT, light-sensitive compounds called photosensitizers (PS) can be encapsulated in liposomes to preferentially enhance their uptake in tumor tissue. A particular wavelength of light can then activate the PS and generate cytotoxic reactive oxygen species, which results in localized destruction of the tumor. Because PSs can be constructed to preferentially localize to tumor sites and light delivery is limited to the area of malignancy, PDT has dual-selectivity.

One type of cancer that will greatly benefit from this therapeutic approach is glioblastoma multiforme (GBM). We hypothesized that PS accumulation and subsequent PDT effectiveness is greatly dependent on the PS used as well as the interval between PS injection and light exposure. To test these hypotheses, three different quantitative fluorescence metrics were used to monitor the effectiveness of PS uptake in subcutaneously implanted tumors one hour and three hours following PS injection. A statistically significant increase in the fluorescence signal was observed following PS delivery in both groups along with a post-PDT decrease due to photobleaching. PDT performed one hour, but not three hours, following PS injection resulted in scar formation and a statistically significant reduction in the tumor volume. The findings suggest that vascular PDT might be more damaging to the tumor compared to intracellular PDT because the amount of PS in the blood at one hour post injection of the PS is higher than the amount at three hours.

Recently, clinical studies have shown the potential success of fluorescence guided resection (FGR) of GBM where pro-drug aminolevulinic acid (ALA) accumulates in tumor cells following intravenous delivery, converts itself into protoporphyrin IX (PpIX) and facilitates demarcation of tumor boundaries, since PpIX is a fluorescent molecule. Given the success of FGR, our current efforts are focused on enhancing the ALA to PpIX conversion specifically in the tumors to enhance the sensitivity of the fluorescence based detection of glioma tumor tissue. We were able to demonstrate that ALA is converted to PpIX at different rates among various glioma cell lines. Currently, we are exploring methodologies to increase ALA to PpIX conversion in cells that have low conversion rate. Overall, these results suggest that whether combined with other treatment options, or as a stand-alone therapy, personalized PS delivery and subsequent PDT could improve FGR and the long-term survival of patients with GBM.
Qualitative Analysis of the March-in Rights Provision of the Bayh-Dole Act

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The high cost of new prescription drugs and other medical products is one of the most important health policy issues of the decade. Excessive health care spending can be damaging to the economy, and affect patients as private and government insurers respond by raising consumer premiums or restricting the benefits offered to their members. High costs are often justified by pointing to substantial investments in researching the products and conducting clinical trials to demonstrate their utility. This explanation for high costs of new medical technology has become particularly controversial when the government funded the key research. Studies have shown that government resources have directly contributed to the discovery of over 150 marketed drugs and vaccines, including some of the most transformative medicines developed in the past twenty years. In these and other cases, some have argued that US patients are in effect paying twice – once for the research and a second time in high prices for the end products.

An equally controversial solution has been offered: government march-in rights. The government retains legal rights in products developed with public funding. While march-in rights were codified in the 1980 Bayh-Dole Act, the scope of their applicability remains unclear, including whether they can be used to reduce consumer prices on products originating from government-sponsored research. In over three decades since the Bayh-Dole Act, petitions for the government to consider march-in rights have been seriously considered only four times—and rejected each time. Given increased recent attention to Bayh-Dole march-in rights, we sought to examine the origins of the march-in rights clause, and identify the bases for the four past petitions to invoke the clause relating to health care products and the rationales for the government’s refusal to intervene.

After collecting the relevant primary documents, we conducted semi-structured interviews with key participants in the development of the legislation and the disposition of past petitions. We targeted 21 potentially relevant opinion leaders. Twelve agreed to participate, and all interviews were conducted between June and July 2013. Median time for telephone interviews was 46 minutes (range: 21-64). Both investigators took notes during the interview, and interviews were recorded and later transcribed. Interview transcripts were analyzed using standard coding techniques and the constant comparative method of qualitative data analysis (NVIVO software package).

Based on the literature review and interviews, policy recommendations were made to both the March-in rights provision and the Bayh-Dole Act.
The activity regulated gene \textit{cpg15} is required for normal development of the excitatory network in the visual cortex

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Experience plays a crucial role in sculpting neuronal connections during development, and aberrations in this process may lead to developmental disorders, such as autism. Patterned neural activity guides the selective stabilization of some synapses and pruning of others in order to form efficient circuits. Activity-regulated growth factors are fundamental to this process of experience-dependent plasticity, but the complex network of molecules and signals that underlie normal development is largely unknown. CPG15, encoded by the activity-regulated gene \textit{candidate plasticity gene 15}, is a small, GPI-linked, extracellular protein that promotes synapse stabilization and cell survival during development. Here we show that knocking out \textit{cpg15} in mice leads to impaired development of the excitatory network in the visual cortex, as well as altered visual function and behavior. Electrophysiology revealed delayed synaptic maturation in the knockout (KO) mice, and KO cells have reduced numbers of mature, mushroom spines. Development of dendritic arbors is also impaired. Visual acuity develops more rapidly in the KO mice, achieving adult levels at an earlier age, yet cortical plasticity appears to be deficient in young KO animals. Our data suggest that CPG15 is required for normal maturation of the excitatory network in the visual cortex and that lack of CPG15 has significant effects on synaptic and morphological development, as well as animal function and behavior.
Evaluating the role of baseline cardiac function assessment in early-stage breast cancer patients

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Anthracyclines and trastuzumab are two of the most effective chemotherapeutic agents widely used to treat breast cancer. However, these therapies can lead to short- and long-term cardiotoxicity. Thus, despite lack of definitive guidelines, screening echocardiograms and radionuclide ventriculograms (RVGs) are often performed prior to chemotherapy to evaluate cardiac function. The clinical utility of these baseline exams has been called into question given that experience suggests these rarely reveal pre-existing cardiac dysfunction or impact treatment decisions in asymptomatic patients who do not have a known history of cardiac problems.

We hypothesized that baseline cardiac evaluation rarely identified abnormalities that would change treatment plans. In addition, in those who had treatment plan changes based on the evaluation, we hypothesize that predictors for pre-existing cardiac abnormalities could be determined and used to identify patients for which baseline cardiac evaluation would be useful. To test our hypothesis, early-stage breast cancer patients seen in consultation for systemic therapy between 2006 and 2011 (n=1067) who had undergone baseline cardiac imaging were identified in the breast cancer registry at Dana Farber Cancer Institute. A retrospective chart review was performed to obtain pre- and post-cardiac evaluation treatment plan information, cardiac evaluation results, and baseline cardiac risk factors.

Of these patients, 600 women had no previous history of chemotherapy, radiation therapy, and cardiac dysfunction, and had clinic notes in the medical record detailing initial treatment plans, followed by an echocardiogram or RVG and final treatment decision. Abnormal results were observed in 13 (2.17%, 1.2%-3.7%) of 600 patients. Of these abnormal results, none led to changes in treatment decisions (e.g., switching to a less cardiotoxic agent), though 2 patients (15.4%, 1.9%-45.5%) received increased monitoring of cardiac function throughout treatment. Modeling to identify predictors for pre-existing cardiac abnormalities was inappropriate given the rarity of such events. Moreover, it would have little utility since treatments do not seem to be changed by baseline cardiac evaluation.

Baseline cardiac imaging evaluation in asymptomatic women without prior cardiac history planning for adjuvant chemotherapy rarely yields an abnormality that prompts change in management. The immediate utility of baseline cardiac imaging is questionable. However, further follow-up to determine the utility of baseline testing among women who go on to have a cardiac problem during or following chemotherapy is warranted.
Palliative Care-Related Knowledge, Attitudes, and Practices among Physicians in Vietnam

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Undertreated pain is a major public health crisis around the world, with 80% of people lacking adequate access to pain relief. In Vietnam, the field of palliative care is growing on several fronts including the education of healthcare workers, policy makers, and the public. Together with the Harvard Center for Palliative Care, curricula were developed to train Vietnamese physicians caring for patients with HIV/AIDS, cancer, and other illnesses on the topics of pain treatment and end-of-life care. Between 2007 and 2012, over 400 physicians across the country participated in five-day training sessions. By analyzing surveys of Knowledge, Attitudes, and Practices (KAP) taken before and after the training, we seek to understand trainees’ existing views and mastery of palliative care topics at baseline. We also aim to evaluate the effectiveness of our training intervention in improving palliative care knowledge in Vietnam.

In a preliminary analysis of trainees who participated from 2007 to 2009, 87 percent agreed at baseline that most cancer patients die in pain and 88 percent that morphine is a medically appropriate treatment for moderate to severe pain. However, 39 percent did not feel comfortable using morphine, and a majority of trainees expressed concerns about its acceptance as a standard treatment, supervisors’ approval, availability, and financial cost to patients. 83 percent of respondents also believed that patients who use morphine for pain or dyspnea can easily become dependent on it. Based on this subset of the data, the percentage of participants who believed that they had adequate training in palliative care increased from less than 14% before the training to 75% afterwards. These findings indicate that palliative care training is a significant need in Vietnam and highlights concerns around the use of opioids in treatment of pain. Future work includes: expanding analysis to the entire dataset; using linear regression analysis to correlate KAP with demographic factors and educational experience; and identifying areas of improvement for our training.

We are also developing an online palliative care curriculum using the Moodle open source courseware platform, enabling future trainees to take the surveys online. Ultimately, we hope this online curriculum can serve as a model to be adapted for palliative care education and collection of KAP data across different sites and languages.
Retrospective analysis of the appearance of the pediatric temporomandibular joint on gadolinium enhanced MRI

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Prolonged and untreated juvenile idiopathic arthritis (JIA) affecting the temporomandibular joint (TMJ) can result in anatomic destruction, deformity and functional limitations, especially in growing children. Early diagnosis may allow treatment to prevent these secondary effects. Recent studies have shown that children with JIA often have asymptomatic involvement of the TMJ with normal clinical examinations. Magnetic resonance imaging (MRI) with gadolinium to assess the signaling intensity of the synovium has recently shown promise as a way of diagnosing asymptomatic TMJ involvement in JIA. Currently, there are no age related normal values of synovial enhancement to make accurate comparisons. The purpose of the current study is to develop age-related standards for TMJ synovial enhancement and to compare the intensity of the synovium on MRI with gadolinium in patients with and without JIA.

In a retrospective cohort study using a database includes patients who had an MRI with gadolinium at Massachusetts General Hospital (MGH) and Massachusetts Eye and Ear Infirmary (MEEI) from 2000 to the present, we chose two groups of patients. Group one was patients with no TMJ pathology who had their MRI taken for other indications. Group two were patients who had been diagnosed with JIA with TMJ involvement. Coronal views of a T1 sequence MRI that contained the greatest cross sectional area of synovium was used to give a numerical score to the intensity of the TMJ synovium and an internal standard (longus capitus muscle) using an image visualization software Synapse®. The enhancement of the MRI was scored based on the ratio of the intensity of TMJ synovium to the intensity of longus capitus muscle.

The enhancement of synovium in MRI of 177 patients from group one has been scored. The same process will be done for patients enrolled in group two. Statistical analysis will be performed using software IBM® SPSS version 20.0. A ROC curve will be used to determine the sensitivity and specificity of MRI with gadolinium. Comparisons will be made between Group 1 and Group 2. Independent 2-sample t tests will be performed for each group with unequal variance assumed. P values will be considered significant if less than 0.05.

Some limitations include the difficulty with standardization of each MRI to show similar amounts of synovium. With the lack of existing normative data, a clinically significant difference in signaling intensity is not known and the study cannot therefore be powered accordingly.
Role of miR-590-5p in regulation of mouse tooth germ morphogenesis

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Understanding the mechanisms involved in tooth morphogenesis is essential for the development of regeneration strategies when teeth are lost or defective in human syndromes. The molecular basis underlying tooth morphogenesis includes the coding and non-coding elements of the genome, such as microRNAs (miRNAs), which are important posttranscriptional regulators during organ morphogenesis. Studies using embryonic mouse models revealed the roles of miRNAs in developing incisors, in the late stages of molar differentiation, and in tooth root formation; yet, the function of miRNAs during molar germ morphogenesis remains unclear. Preliminary expression profiling studies comparing the expression of microRNAs in multiple embryonic organs have revealed novel, uncharacterized microRNAs, such as miR-590-5p. In silico analysis suggests that miR-590-5p targets components of the gene regulatory network involved during molar germ morphogenesis. However, the role of miR-590-5p during molar germ morphogenesis remains unknown.

This project aims to define the regulatory role of miR-590-5p during molar germ morphogenesis. We hypothesized that miR-590-5p is differentially expressed, and regulates components of the gene regulatory network involved in molar germ morphogenesis. In order to test this hypothesis, we analyzed the expression of miR-590-5p and its predicted targets throughout the embryonic mouse molar development, and analyzed the morphogenetic changes during molar germ morphogenesis. Loss-of-function studies were performed using inhibitors of miRNAs (antagomirs) transfected via nanoparticles in explanted embryonic mandibles containing the molar tooth germs.

Gene expression analysis by qPCR confirmed that Chd7 (a predicted target for miR-590-5p), Sox2 (which is a Chd7 binding partner), and Bmp4 (a component of the molar germ gene regulatory network), were upregulated after miR-590-5p loss-of-function using antagomirs, whereas other miR-590-5p predicted targets did not change. These results indicate that miR-590-5p specifically regulates Chd7 during early molar germ morphogenesis. Frozen sections of the molars in explanted mandible cultures, followed by fluorescent immunohistochemistry and EdU-incorporation, showed an abnormal molar morphogenesis and defective cell proliferation, respectively, after miR-590-5p loss-of-function.

These results strongly suggest a regulatory role for miR590-5p during molar germ morphogenesis. Further studies include addressing the role of Chd7-Sox2 in regulating Sonic Hedgehog (Shh) signaling during molar germ morphogenesis, and rescue of morphogenesis using exogenously added recombinant Shh in mandibular explants treated with miR-590-5p antagonirs. These studies provide mechanistic insights into miRNA regulation of early molar morphogenesis, with further implications in molar tooth regeneration and miRNA-based therapies.
The Effect of Fine Particulate Matter on Metabolic Dysfunction

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Background: Air pollution exposure has been linked with cardiovascular and pulmonary morbidity and mortality, but mechanisms mediating this effect remain elusive. Metabolic syndrome comprised of at least three of the following individual conditions—obesity (body mass index (BMI) >30), hypertriglyceridemia (≥150 mg/dl), hypertension, high fasting blood sugar (≥110 mg/dl), and reduced high-density lipoprotein (HDL) cholesterol (<40 mg/dl)—is also associated with increased cardiovascular and pulmonary disease.

Objectives: To prospectively examine the effect of atmospheric fine particulate matter on the development of metabolic syndrome and on the individual conditions that comprise the metabolic syndrome.

Methods: 674 elderly men (mean age 69±7 years) from the VA Normative Aging Study longitudinal cohort were included in the study. The association between long-term PM$_{2.5}$ exposure and metabolic dysfunction was estimated using Andersen-Gill Cox proportional hazards models.

Results: The hazard ratio associated with an average annual atmospheric fine-particulate matter with diameter ≤ 2.5 µm (PM$_{2.5}$) increase of 1 µg/m$^3$ were 1.518 for risk of developing metabolic syndrome (p=0.0006), 1.321 for elevated fasting blood glucose (p=0.0069), 1.812 for high BMI (p=0.0017), 1.462 for hypertension (p<0.0001), 1.905 for hypertriglyceridemia (p<0.0001), and 2.478 for low HDL cholesterol (p<0.0001).

Conclusions: Long-term PM$_{2.5}$ exposure may increase cardiovascular and pulmonary disease though increased risk of metabolic dysfunction.
Clinical and Regulatory Features of Drugs Not Initially Approved by the US Food and Drug Administration

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Drug innovation in the United States is an unpredictable process that sees many promising new therapeutic possibilities drop out of contention at early stages of development. By contrast, non-approvers by the US Food and Drug Administration (FDA) after a new drug application (NDA) or biologics licensing application (BLA) has been submitted to the agency are less common. Considering the resources already spent on large Phase II and Phase III trials by this time, FDA non-approval decisions are particularly controversial. Thus, we sought to assess the details of FDA decision-making leading to non-approvals to determine the reasons for the rejection and whether certain characteristics of non-approved medications predicted likelihood of approval in subsequent rounds of FDA review.

Since the FDA does not disseminate the names of non-approved drugs, we gathered a list of unapproved drugs by analyzing the transcripts of all FDA advisory committee meetings from 2007 to 2009 in which novel NDAs and BLAs were reviewed. FDA advisory committees review most of the important drug applications assessed by the agency, and FDA generally follows the recommendations provided by these committees. For applications that received a non-approval letter from the FDA, we obtained descriptive characteristics of interest, including the current approval status of the drugs, their proposed indication and therapeutic category, and the reason(s) for failure.

Our study found that half (27/52, 52%) of new drugs and biologics evaluated by FDA advisory committees between 2007 and 2009 were unapproved in the first cycle of review. The most common (non-mutually exclusive) contributors to the non-approval decision were excessive safety risk (13, 48%), efficacy concerns (7, 26%) and labeling issues (4, 15%). An additional five drugs (19%) were judged to have both efficacy and safety concerns. Eleven of these initially unapproved drugs were eventually approved, including 8 of the 13 applications (62%) that were initially unapproved due at least in part to safety reasons (but not to efficacy concerns). By contrast, only one of the 12 applications initially unapproved due to at least in part to efficacy concerns was later approved.

Our findings show that a high number of drugs were found to have important safety and/or efficacy problems at the time of submission of the new product application to the FDA. Products with initial safety concerns were much more likely to be approved eventually than drugs with efficacy concerns.
Angiotensin II and aldosterone potentially induce vascular smooth muscle cell calcification by decreasing expression of the microRNA-30 family

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Vascular calcification is highly prevalent and is associated with a 3-4-fold increased risk for cardiovascular morbidity and mortality. Although once viewed as a consequence of calcium/phosphate imbalance and deposition, it is now recognized that vascular calcification is a highly regulated process that recapitulates skeletal bone formation. The central role of vascular smooth muscle cell dedifferentiation to assume an osteoblast-like phenotype and promote vascular calcification has been demonstrated. Osteoblast-like smooth muscle cells have decreased expression of smooth muscle cell-specific markers, such as myocardin, smooth muscle myosin heavy chain and smooth muscle alpha-actin, and increased expression of bone-related proteins, including alkaline phosphatase and osteocalcin.

MicroRNAs (miRs) are small noncoding sequences of approximately 22 nucleotides that bind to the 3’-untranslated regions (UTR) of mRNAs to silence gene expression by inhibiting translation or promoting degradation of target mRNAs. MiRs are complementary to the target mRNA sequence and only require complete complementarity of a 7-mer or 8-mer “seed sequence” for binding to occur. There is evidence to support a role for miRs in vascular calcification as miRs have been implicated in smooth muscle cell phenotype switching, and prior work from our laboratory has demonstrated miR regulation of Runx2, a master osteoblast transcription factor, in vascular smooth muscle cells.

Angiotensin II and aldosterone play critical roles in vascular function, and evidence suggests that they can cause vascular calcification in certain disease states such as CKD. To date, the relationship between angiotensin II and aldosterone to vascular smooth muscle expression of miRs remains unknown. Our previous research suggests that inhibition of miRs in the miR-30 family promote vascular smooth muscle calcification. We, therefore, hypothesize that angiotensin II and aldosterone downregulate the expression of certain miR-30s to induce calcification of vascular smooth muscle cells. Once candidate miR’s have been selected, we will modulate their expression and examine signaling pathways and vascular calcification in vitro.
Evaluation of the Congruence Between Clinicians’ Post-encounter Notes and Actual Conversations with Patients about End-of-Life Care

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There is a disconnect between the type of care that patients desire at end of life and the type of care they receive. For example, while 86% of Americans say that they would prefer to die at home, only 25% are able to do so. Although most seriously ill patients prefer to avoid “heroic” interventions, 46% of them received mechanical ventilation within three days of death despite being asked about their preferences. Prior studies have examined how accurately physicians’ documented patient values and goals. Therefore, the goal of this project is to compare the content of recorded conversations to documentation in physician notes.

All Dana Farber Cancer Institute physicians and nurse practitioners who work in sarcoma, head and neck, breast, neuro-oncology, GU, GI, and melanoma have been invited to participate in the study. Adult patients of participating physicians with a prognosis of less than one year are recruited using the ‘surprise’ question. Once patients are enrolled, their physicians are prompted to have structured conversation about values and goals at end of life. To date, eight conversations have been recorded and transcribed. For this study, we are aiming for a total of forty patient recordings. Initially, we planned that conversations be assessed based on the errors of commission and omission in the end-of-life care module. Although we began with this quantitative method to assess the quality of the conversation, with four raters, (two medical students and two physicians, we determined that our kappa scores (% agreement) was too low to continue with this method and it is necessary to take a more qualitative approach. Although we only have about 10% of the total data gathered, some trends have emerged. Most interestingly, the quality of EOL conversation does not always correlate with the quality of the documentation. Physicians who had longer, more in depth discussions with patients sometimes poorly documented their visits while others who had very brief conversations documented the visit accurately. More data is needed to determine next steps.
Physicians and Patients Assessment of the Value of Medical Care

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Introduction: Healthcare delivery systems have recently focused on the concept of value delivery as a way of optimizing patient experience and outcomes while containing costs. Value, defined as patient health outcomes per dollar spent, is a concept that providers, patients and policymakers embrace. Although campaigns like the ABIM Foundation’s Choosing Wisely target both physicians and patients in order to promote high-value care, there has been little investigation of whether physicians and patients interpret value similarly. Based on recent evidence that patients who received unnecessary imaging for lower back pain reported higher satisfaction with their care, we hypothesized that doctors and patients may have different conceptions of what constitutes high- or low-value clinical care.

Methods: We conducted a cross-sectional survey of 203 primary care patients and 47 primary care physicians at three academic medical centers (physician recruitment is ongoing). The questionnaire included two vignettes to assess perspectives on the value of healthcare, based on opportunities to improve the value of care identified by the Choosing Wisely campaign. Vignette A described a patient with a tension headache who is concerned about brain cancer and requests imagining for his headache that the doctor does not think is necessary. The patient then sees another doctor and receives a CT scan. Vignette B described a patient with a three-day viral infection who requests and is denied antibiotics. We performed cognitive interviewing and pilot testing to refine scale items. We also assessed attitudes towards healthcare costs. Descriptive statistics were used to describe frequencies. Chi-square and Fisher’s exact test were used to compare proportions between patients and physicians.

Results: The overall response rate was 64% (203/319) for patients and 42% (47/112) for physicians. Among patients, 35% were men, 63% were white. Patients more often reported that imagining for a tension headache represented high-value care than doctors (61% vs. 11%), and less often reported that denying antibiotics for a viral infection represented high-value care (67% vs.100%). Additional descriptive and comparative statistics of our results are planned to assess how the same respondent may value different types of care and what aspects of care drive these perceptions.

Conclusion: Preliminary data indicate that there is disagreement between physicians’ and patients’ perceptions of the value of care. Patients are more likely to under-rate high value care and over-rate low-value care. Addressing these discrepancies will be critical to our ability to contain healthcare costs and deliver high value care to patients.
Promoting Healthy Diets on an American Indian Reservation Through Direct Access to Nutrition

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The residents of the Fort Peck Indian Reservation in northeast Montana face disproportionately high levels of diabetes, hypertension, and obesity. While these diseases are complex in etiology, there is a general consensus among local healthcare providers that this disparity is due in large part to the chronic malnutrition that results from a lack of healthy food options. To address this issue we produced a series of short videos that sought to empower local youth to create their own sources of healthy food by growing modern food in a garden and foraging for traditional Sioux and Assiniboine foods in the wild. To ensure that the videos would be acceptable to local youth we recruited, trained and managed a film crew of eight 11-14 year olds. Over a five week program this film crew was responsible for researching the featured foods, writing the scripts, managing the sound and lighting, directing, filming, acting, and interviewing key informants for each movie. To test the educational value of the program, we created a twelve question survey to measure participant knowledge of filmmaking as well as modern and traditional Sioux and Assiniboine foods and administered it on the first and last day of the program. Average total scores improved from 59% to 77% over the course of the program. Participant scores climbed from an average of 61% to 73% on the traditional foods section and from 58% to 81% on the filmmaking section. Two participants scored lower on one section on the exit survey; leading to a lower total score for one of them.

While the scores we received seem to indicate that it is possible to utilize a film project to engage and educate youth around healthy eating, it is important to recognize that this project and the films generated from it are only the first step in an ongoing effort to increase access to healthy foods for youth on the Fort Peck Indian reservation. Next steps include increasing access to gardening space for local youth with appropriate oversight from a community based organization.
Listening to the Patient Voice: Qualitative Interviews on the Patient-Centered Medical Home

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Patient voices must be integrated into primary care delivery innovations. Building a higher-value healthcare system requires innovations in primary care that improve quality and increase access. The patient-centered medical home (PCMH) is the prevailing model for achieving these improvements. Innovations in the delivery of primary care are intended to improve the experience of patients. However, direct patient feedback on novel PCMH delivery methods is difficult to capture and integrate into ongoing practice improvement.

The purpose of this study was to qualitatively examine patients’ attitudes toward changes that accompany the PCMH at Brookside Community Health Center. Semi-structured interviews were conducted with 22 Brookside patients recruited from the adult medicine department. Interviews covered domains that included relationships, teams, shared work, and overall impressions of care at Brookside. Interview data has thus far been inductively analyzed to identify themes that arose from patients’ responses to standardized questions. Further analysis will utilize grounded theory to develop a theory of patients’ attitudes toward the PCMH. Later deductive analysis will attempt domain-specific themes that suggest

Inductive analysis has identified five themes: (1) Comfort with Brookside (2) High valuation/fear of losing relationships with providers (3) General optimism and specific skepticism of new staff roles (4) affirmation of articulated team ideals and (5) trust in providers and Brookside translating into optimism about innovations. Themes were not uniform across patients, and have yet to be analyzed for patterns according to age and gender.

Preliminary results indicate opportunities to reach out to patients and articulate the aims and methods of PCMH innovations. Encouraging providers to discuss these innovations with patients and solicit their feedback should be included in process improvement efforts of community health centers undergoing PCMH transformation. Further methods to evaluate and incorporate patients’ perspectives should be employed in ongoing practice improvement efforts.
The Development of a Pediatric Hospice Program: Training Adult Providers in Pediatric Care

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Issues: Children have limited access to quality hospice care; these children and their families suffer unnecessarily at the end of life. Few existing hospice programs have dedicated pediatric teams even though pediatric patients have unique needs at the end of life and providers report feeling inadequately trained to care for these children.

Description: As part of the development of a new pediatric hospice program in Boston, we created an education program to train interdisciplinary teams of adult hospice providers in pediatric end of life care. Our curriculum consists of thirteen modules taught through a variety of teaching methods including lectures, discussions, actors, and role-play. These modules cover a range of topics from communication with children to treatment of pediatric end of life symptoms to spiritual care and support for the family resulting in a comprehensive introduction to pediatric care. This education program is part of a larger effort by Hospice of the North Shore and Greater Boston to create an adaptable and sustainable model for the delivery of pediatric hospice and palliative care that can be replicated in other settings, nationally and internationally.

Lessons Learned: We hypothesize that this education program will improve learners’ knowledge, skills, and attitudes about pediatric care. We are currently analyzing data from pre and post assessments and focus groups to evaluate our hypothesis. Nineteen learners from the two-day program and thirty learners from the one-day program completed assessments before and after training and will complete an assessment again six months after completion. The assessments consist of 36 questions designed to evaluate achievement of specific objectives for each module taught. Preliminary analysis shows that participants’ knowledge improved and their self-reported confidence level in various aspects of pediatric end of life care increased significantly.

Recommendations: The existing infrastructure of adult hospice programs is an untapped resource that can be utilized to increase access to pediatric hospice care, both nationally and internationally. Providers are experienced in end-of-life care and can be trained to transfer this knowledge to the care of pediatric patients. Increasing the number of providers trained in pediatrics will improve access to care for pediatric patients and decrease unnecessary suffering for patients and families at the end of life.
Reducing Neonatal Mortality in Rwanda: Baseline Patient Satisfaction with Antenatal and Maternity Care

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Neonatal deaths are one of the strongest contributors to child mortality in Rwanda. In response to this pressing need in the field of neonatal health in the country, the All Babies Count (ABC) Initiative – led by Partners in Health Rwanda, Inshuti Mu Buzima – aims to promote newborn survival through improving maternal and neonatal health services. The strategies that the ABC Initiative will employ to reach this goal include: 1) training and mentorship of health workers; 2) strengthening health systems currently in place; and 3) a quality improvement strategy involving learning collaboratives.

One essential measure of the success of such a program is the level of patient satisfaction with the services provided. To promote neonatal health, it is essential that pregnant women access antenatal and maternity care and that parents bring their newborn children to a health facility when they fall ill. Mothers who have greater satisfaction with health services may be more likely to seek health care. Thus, improving patient satisfaction with pregnancy and maternity health services is expected to have a positive effect on access to care for pregnant women and newborns – and therefore on neonatal health.

The current project aims to assess the baseline level of satisfaction with antenatal care (ANC) and maternity services at facilities participating in the ABC Initiative, with the eventual goal of analyzing the impact of this initiative on patient satisfaction by comparing baseline to post-intervention data. Health facilities in southern Kayonza and Kirehe districts that provide ANC and maternity services (8 in Kayonza, 16 in Kirehe) will participate. Women who have received ANC services or have delivered at the facility will be asked to complete a verbally-administered survey regarding their satisfaction with the services received. Data collection is ongoing.

The results of this survey will be analyzed for the primary outcome – overall satisfaction with the services received – in addition to secondary outcomes that will track components of maternal knowledge, health-seeking behaviors, and satisfaction with health worker communication and service quality. This assessment of baseline levels of satisfaction with ANC and maternity services will help identify areas for improvement over the course of the ABC Initiative and will provide a starting point for an analysis of changes that occur as a result of the initiative. A program successful both at improving health services for mothers and newborns and at increasing patient satisfaction with those services could serve as a scalable model for the region.
Polymorphisms of \textit{MUC16} (CA125) and \textit{MUC1} (CA15.3) in relation to ovarian cancer risk and survival

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Objective: To examine single nucleotide polymorphism (SNPs) in \textit{MUC16} (CA125) and \textit{MUC1} (CA15.3) in relation to ovarian cancer risk and survival.

Methods: We genotyped germline variants of \textit{MUC16} (rs2547065, rs1559168, rs12984471, rs2121133) and \textit{MUC1} (rs2070803, rs4072037, rs1045253) using samples collected from 758 ovarian cancer cases and 788 controls enrolled in the New England Case-Control Study between 2003 and 2008. We calculated age-adjusted odds ratios (OR) and 95% confidence intervals (CIs) for disease risk using unconditional and polytomous logistic regression and hazard ratios (HR) for survival using Cox proportional hazard ratios. In a subset of cases, we compared log-normalized CA125 values by genotype using generalized linear models.

Results: Cases homozygous for the variant allele of \textit{MUC16} SNP, rs12984471, had poorer overall survival (log-rank \(p=0.03\)) and higher CA125 levels, especially cases over age 65 (\(p=0.01\)). For \textit{MUC1} SNP, rs4072037, women homozygous for the G variant had a non-significantly decreased risk for serous invasive types but elevated risk for serous borderline tumors, mucinous borderline and invasive tumors, and endometrioid tumors. Women with the variant allele of \textit{MUC16} SNP, rs2547065, especially those who were homozygous had an elevated risk for ovarian cancer; but this association was not confirmed in an independent dataset.

Conclusion: This targeted screen of seven polymorphisms of \textit{MUC16} and \textit{MUC1} genes failed to identify and confirm effects on ovarian cancer risk overall. However, there may be effects of \textit{MUC16} rs12984471 on survival and \textit{MUC1} rs4072037 on risk for histologic types of ovarian cancer other than invasive serous. Further study is warranted.
Disease Responsive Materials for Orthopedic Applications

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Optimizing the interaction between cells, environment, and materials is the next frontier for improving current methods of healing. While the earlier standard for implantable materials was bio-inertness (having no negative effects on the body), more recently this standard has shifted to biocompatibility and bio-interactivity: materials are expected to work with the microenvironment and the native (or introduced) cells, to facilitate the goals of drug delivery and/or healing. Given the variability in tissue microenvironments, a single material cannot be appropriate for all conditions, and a more feasible approach is to develop a composite material whose properties can be modified to meet different demands. Materials for orthopedic applications are especially challenging because of repeated, high-intensity loading. We believe a hydrogel reinforced with exfoliated clay nanoparticle is up for the challenge. Clay nanoparticles can interact with polymers to enhance mechanical properties; additionally, recent research has documented the osteo-inductive properties of exfoliated clay nanoparticles.\(^1,2\) Combining clay's unique properties with hydrogels bio-inductive properties would create composite ideal for orthopedic applications. Furthermore, parameters such as clay concentration and size can be varied to create different microenvironments appropriate for diver orthopedic therapies ranging from focal cartilage defect treatment to spinal fusion promotion.
Changes in Specificity of HIV-1-specific CD4 T Cell Responses following Acute HIV-1 Clade C Infection

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Background: More than 3 decades into the epidemic, there are over 34 million HIV-infected individuals worldwide and no effective vaccine. Although emerging evidence has highlighted the important role that HIV-specific CD4 T-cells play in immunological regulation of HIV, there are relatively few studies that have methodically investigated which specific HIV protein subunits and peptides from the entire array of proteins expressed by HIV (i.e. HIV proteome) elicit a CD4 T-cell response, a phenomenon known as immunodominance. Furthermore, there have been no longitudinal studies of changes in immunodominance from acute infection onwards -- a key piece of information in the rational design of an HIV vaccine.

Objective: We investigated the frequency, specificity, and immunodominance profile of CD4 T-cell responses to the entire HIV-1 clade C proteome in a unique cohort of South African patients acutely infected with HIV-1 clade C and followed longitudinally after primary infection.

Methods: Patients from a previous study of primary HIV infection were included in our study if they had an adequate number of archived peripheral blood mononuclear cells (PBMC’s) collected at acute infection and at 2 time-points after acute infection. All 3 time-points were assayed in parallel to ensure longitudinal consistency and comparability. For the assay, we enriched cryopreserved PBMC’s for CD4 T-cells using magnetic bead depletion techniques. We then incubated 100,000 cells with oligopeptides in each well of a 96-well ELISpot plate with an antibody-coated membrane that captured IFN-gamma from activated T-cells. After washing off the cells and developing the plate using a biotinylated detection antibody, the plates were read and analyzed using an AID ELISpot reader and software to determine the number of positive responses in each well. In the screening matrix oligopeptide panel, each of the 410 18-mer overlapping peptides composing the HIV proteome were present in at least 2 wells which is being analyzed with a matrix resolver software to suggest candidate immunodominant oligopeptides. Confirmatory testing of the same samples with single peptides to rule out false positives will be conducted in late 2013.

Results: We completed ELISpot assays on 8 patients for a total of 24 time points; whole HIV proteome screening data is currently available for 3 of the patients. Preliminarily, there appears to be an initial response to several HIV peptides during acute infection that expands a month after acute infection and contracts approximately 1 year after acute infections. The magnitude of HIV-1 specific CD4 T cell responses ranged from 9 to 19 spot per 100,000 cells (median 17). Most responses are in the Gag and Nef region of the proteome. Analyses of specific peptides and changes in the HIV-1 specific CD4 T cell response over time are still being conducted.
The effect of food service interventions on the calories of food sold

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In 2009-10, more than one-third of adults 20+ years of age and 17% of children ages 2 to 19 years were obese. To address this epidemic, various forms of population level interventions have been implemented and tested. Pricing strategies which raise the price of unhealthy foods, i.e. taxation, or decrease the price of healthy foods, i.e. subsidies, have become quite popular. While previous studies demonstrated the potential of such interventions, they typically examined the change in sales of different food groups only in isolation. Consumers may be purchasing more healthful foods without any change in calorie consumption, a prerequisite for weight loss.

For this study, we examined the effect of a beverage intervention, conducted in a large employer’s cafeteria, on food and total calories sold within the cafeteria. The intervention had two components: 1) a 1 cent per ounce increase in the price of all sugary beverages of ≥ 150 calories, and 2) a reorganization of beverages to present them by calorie content. Prior work has demonstrated that high calorie beverage purchases declined during each of the intervention phases. For this analysis, we hypothesized that both the price increase and reorganization of beverages decreased the total calories sold in the cafeterias. In other words, we hypothesized that customers dining in the cafeterias did not purchase more food calories to offset the benefit of their reduced purchases of high calorie beverages.

We collected all food and beverage sales data from the cafeteria from September 2011 to June 2012. This time period overlapped with our intervention: price increase on high-calorie sugary beverages from October to December 2011; reversion to baseline prices during a washout from January to February 2011; display of beverages by calorie content from March to May 2012. The calories of food items were obtained either through the food service provider, package labels, USDA or calorie tracking applications. We used the sales of food items as proxy for the food eaten, with the assumption that the customers of the cafeteria were relatively static. For the analysis, we will use an interrupted time series approach to examine the effect of the interventions, compared to the baseline period, on total food sales and calories purchased for all items in the cafeteria.
Optimal systolic blood pressure target, time-to-intensification and time-to-follow-up in the treatment of hypertension

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Importance. The optimal systolic intensification threshold, time to medication intensification after the first elevated blood pressure measurement, and time to blood pressure follow-up after medication intensification in the management of hypertension are unknown.

Objective. To establish the systolic intensification threshold, time-to-intensification and time-to-follow-up that is associated with the lowest risk of cardiovascular events or death among adults with hypertension.

Design. Retrospective cohort study.

Setting. United Kingdom.

Participants. 81,178 patients with hypertension from The Health Improvement Network nationwide primary care research database.

Main Outcome Measures. We analyzed the relationships between the systolic intensification threshold, time-to-intensification and time-to-follow-up over the course of a 10-year treatment strategy assessment period and time to first acute cardiovascular event or death. The Cox regression model was adjusted for age, sex, smoking status, socioeconomic deprivation, history of diabetes or cardiovascular disease, Charlson Comorbidity Index, body mass index, medication possession ratio, and blood pressure during the treatment strategy assessment period.

Results. During a median follow-up of 3.1 years after the treatment strategy assessment period, 8,362 participants experienced acute cardiovascular event or death (10.3%). No difference in outcome risk was seen between systolic intensification thresholds of 130-150 mmHg, while systolic intensification thresholds greater than 150 mmHg were associated with progressively greater risk. Outcome risk increased progressively from the lowest (0-1.4 months) to the highest quintile of time to medication intensification. The highest quintile of time to follow-up (>2.7 months) was also associated with increased outcome risk.

Conclusions and Relevance. Systolic intensification threshold higher than 150 mmHg, delays of greater than 1.4 months before medication intensification following systolic blood pressure elevation, and delays of greater than 2.7 months before blood pressure follow-up after each antihypertensive medication intensification are associated with increased risk for acute cardiovascular event or death. These findings support the importance of timely medical management and follow-up in the treatment of patients with hypertension.
Merkel Cell Carcinoma Clinical Presentation and Survival: a Population Study

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Merkel cell carcinoma (MCC) is a rare but aggressive skin cancer. It has high rates of local recurrence and regional lymph node metastases, and a mortality rate more than double that of melanoma. With the incidence of MCC rising in the last few decades, it will impact an increasing number of people, particularly the aging population. Even though diagnoses, treatment, and prognosis have improved in the last few decades, there are few large epidemiological studies capturing the consequences of these advancements. The purpose of this study is to analyze the clinical presentation and survival of a large group of patients to better understand how MCC typically presents and what factors can lead to improved survival outcomes.

We conducted a retrospective review of 227 patients with MCC treated at Brigham and Women’s Hospital, Massachusetts General Hospital, and Dana Farber Cancer Institute between 2003 and 2013. Records of patient charts and pathology reports were referenced for patient demographics, presentation and stage of the disease at initial diagnosis, primary tumor characteristics, and treatment delivered.

The review showed that over 95% of patients were older than age 50 at diagnosis, with the mean age being 71. 42% of the patients had a previous history of other skin cancers, including melanoma, basal cell carcinoma, or squamous cell carcinoma. 9% were immunosuppressed at the time of diagnosis. The top presenting anatomic locations of primary tumors were the head and neck, lower limb, and upper limb. However, 14% of patients presented with nodal disease without a skin primary. The most frequent treatment combinations given were surgical excision with sentinel lymph node biopsy (53%) followed by radiation to the primary tumor and nodal bed (49%). 36% of patients were treated with chemotherapy.

These results suggest that MCC is likely to present in the elderly, in those with previous incidences of skin cancer, and in areas routinely exposed to UV sunlight. The current standard of treatment for most patients at our institution seems to be surgical excision with follow-up radiation. Variations occur when patients cannot tolerate surgery or radiation, have advanced disease requiring chemotherapy, or have specific patient characteristics that make adjuvant chemotherapy justifiable.
Cleavage of the Anaplastic Lymphoma Kinase in Neuroblastoma

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Neuroblastoma, a tumor of the sympathetic nervous system, is responsible for 15% of all childhood cancer deaths. Recent studies have identified activating, small molecule inhibitor-sensitive mutations in the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase. Consequently, this finding has led to the development and clinical trials of several ALK inhibitors for this subgroup of patients. However, ALK mutations are present in only 10% of neuroblastomas; by contrast, wild-type ALK is expressed in more than 90% of neuroblastomas and is activated in 60% of these. This points to a mutation-independent mechanism of ALK activation.

One such mechanism has been suggested by previous work in the George Laboratory, which showed that proteolytic cleavage of the ectodomain of ALK promotes the proliferation of BaF3 cells. I hypothesized that proteolytic cleavage of ALK in neuroblastoma cells, leading to the shedding of the ALK ectodomain, would result in the production of an activated, truncated, membrane-bound ALK fragment, and represent a functionally significant event in promoting the proliferation of neuroblastoma cells.

To test this hypothesis, I transduced SK-N-AS neuroblastoma cells, which express low endogenous levels of ALK, with either a GFP control, or the wild-type (ALK-WT), cleaved (ALK-p140), or cleavage-impaired (ALK-L5) ALK constructs. Expression of ALK-p140 augmented the growth of SK-N-AS cells to levels similar to those of SK-N-AS cells expressing ALK-WT. By contrast, expression of ALK-L5 in SK-N-AS cells showed no significant difference in growth compared to SK-N-AS cells expressing GFP control. Immunoblotting analyses showed phosphorylation of the activating ALK-Y1604 residue in SK-N-AS cells overexpressing either ALK-p140 or ALK-WT, but not in those overexpressing GFP or ALK-L5, suggesting that cleaved ALK confers a growth advantage to neuroblastoma cells via increased ALK activity.

I next validated a monoclonal antibody directed against the shed ectodomain of ALK. As the mechanism underlying ALK cleavage is unknown, this antibody would be used to assess levels of ALK cleavage in neuroblastoma cells following shRNA depletion of candidate proteases to identify mediators of ALK cleavage. Immunoblotting and immunocytochemical analyses demonstrated specificity of the antibody to the shed portion of ALK. Additionally, immunoprecipitation experiments using this antibody showed pull-down of only full-length, uncleaved ALK. Together with the finding that ALK-p140 augments the proliferative potential of neuroblastoma cells, results from this screen will help elucidate the functional significance and mechanism of ALK cleavage in driving neuroblastoma malignancy, and may reveal therapeutic possibilities for neuroblastoma treatment in the future.
A Study of Trust in the Patient-Centered Medical Home

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Background: The patient-centered medical home (PCMH) is an innovative effort to improve the value and efficiency of healthcare in the United States. It is a team-based model of healthcare delivery predicated on seven key principles: personal physician directed comprehensive team-based practice; whole person orientation; coordinated care integrated across settings; quality and safety, including optimal utilization of evidence-based techniques and information technology to enhance communication, performance measurement and patient education; personal physician trained to provide first contact and continuous care; enhanced access; and reformed payment structure.

While the number of programs of this kind in the United States continues to grow, little is known about what effects this model of care has on the physician-patient relationship. We assessed the effects of the PCMH on patient trust, and characterized the relationship between patients’ trust in their medical practice and health outcomes. We hypothesized that the PCMH encapsulates three key innovations that might reasonably be expected to bear on the flow of relationships and trust in medicine: Patient-centeredness; team-based coordinated care; and pay-for-performance systems.

Methods: We conducted a cross-sectional survey of primary care patients from one PCMH (BWH South Huntington) and from one non-PCMH practice. The survey included validated measures of patient trust in the practice and sociodemographic information. Patients’ HbA1c, cholesterol, BMI, time in practice, hospital admissions and readmissions were extracted from the electronic medical record. The survey also included open-ended questions about patient trust. Descriptive statistics were used to describe frequencies. Chi-square and Fisher’s exact test were used to compare patient trust between the two types of medical practices.

Results: Data collection and analysis is ongoing. The overall response rate to date was 97% (81/83). Fifty-two percent of respondents were Caucasian, 22% African American, 15% Hispanic or Latino, 5% Asian or Pacific Islander. Sixty-two percent were women. Respondents’ mean trust score was 27 out of 30. Frequency analysis of recurrent themes in responses to qualitative questions suggest that key determinants of patient trust in their PCMH include patient comfort; clinician elicitation of patient concerns; caring; thoroughness; safety; transparency; honesty; and timeliness.

Conclusions: Preliminary data indicate high levels of patient trust in the PCMH studied. Respondents’ trust in their PCMH was associated with both practice and physician characteristics. Understanding how a PCMH influences patient trust can lay the groundwork for optimizing provider-patient relationships and improving healthcare delivery in an era of rapidly transforming approaches to medical care.
Thalamic Neuronal Loss in Periventricular Leukomalacia

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Periventricular leukomalacia (PVL) is the major type of brain injury in premature infants, with cognitive deficits as the most common neurological sequelae. However, the pathogenesis of these cognitive problems remains unclear. Clinical observations have shown that the thalamus is vulnerable to perinatal brain injury, specifically at the mediodorsal and reticular nuclei. These two regions are dense in GABAergic inhibitory neurons thought to be involved in higher cognitive functions. The goal of this project was to determine if the thalamic damage in PVL is specific to the GABAergic neuron subpopulation, thus providing a possible mechanism for cognitive deficits in patients.

We hypothesized that there is a disproportionately increased loss of inhibitory neurons in the mediodorsal and reticular nuclei in an animal model of PVL. To quantify neuronal number, we performed unbiased stereology on both sham and PVL tissue. PVL brain injury was modeled in rats by inducing hypoxia-ischemia via laparotomy and uterine artery occlusion. Collected brain tissue was immunolabeled for parvalbumin (PVA), a marker of GABAergic inhibitory neurons, and NeuN, a pan-neuronal marker. Both sham and PVL groups each had a sample size of \( n=4 \), and for each sample, 100+ frames were systematically counted using stereological techniques. Samples were analyzed for nuclei volume, neuron load, and average cell body size. In the reticular nuclei, NeuN load in PVL samples was 25.2% lower than that in sham samples \( (p=0.0494) \). Additionally, PVA load was 37.6% lower in PVL samples versus sham samples \( (p=0.0118) \). The greater loss in PVA load suggests that damage in the reticular nuclei is concentrated on a subpopulation of GABAergic inhibitory neurons. With both NeuN and PVA immunolabeling, both reticular nuclei volume and average cell body size were not significantly different between sham and PVL. In the mediodorsal nuclei, PVL samples had a 51.0% decrease in NeuN load compared with sham samples \( (p=0.0108) \). There was no significant difference in mediodorsal nuclei volume \( (p=0.055) \) or average cell body size \( (p=0.204) \). Inhibitory neurons in the mediodorsal nuclei did not label well for either PVA or neuropeptide Y, a marker for another subpopulation of inhibitory neurons.

Our study not only translates the clinical findings of neuronal damage in thalamic nuclei to a PVL rat model, but it also demonstrates that this thalamic damage is specific for a GABAergic neuron subpopulation. Damage to this subpopulation of neurons could provide an underlying mechanism for the cognitive deficits often observed in patients with PVL.